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# ORIGIN AND CONSEQUENCES OF NECROINFLAMMATION

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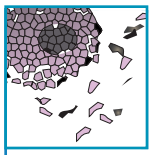


**Sarhan M, Land WG, Tonnus W, Hugo CP, Linkermann A.** Origin and Consequences of Necroinflammation. *Physiol Rev* 98: 727–780, 2018. Published February 21, 2018; doi:10.1152/physrev.00041.2016.—When cells undergo necrotic cell death in either physiological or pathophysiological settings in vivo, they release highly immunogenic intracellular molecules and organelles into the interstitium and thereby represent the strongest known trigger of the immune system. With our increasing understanding of necrosis as a regulated and genetically determined process (RN, regulated necrosis), necrosis and necroinflammation can be pharmacologically prevented. This review discusses our current knowledge about signaling pathways of necrotic cell death as the origin of necroinflammation. Multiple pathways of RN such as necroptosis, ferroptosis, and pyroptosis have been evolutionary conserved most likely because of their differences in immunogenicity. As the consequence of necrosis, however, all necrotic cells release damage associated molecular patterns (DAMPs) that have been extensively investigated over the last two decades. Analysis of necroinflammation allows characterizing specific signatures for each particular pathway of cell death. While all RN-pathways share the release of DAMPs in general, most of them actively regulate the immune system by the additional expression and/or maturation of either pro- or anti-inflammatory cytokines/chemokines. In addition, DAMPs have been demonstrated to modulate the process of regeneration. For the purpose of better understanding of necroinflammation, we introduce a novel classification of DAMPs in this review to help detect the relative contribution of each RN-pathway to certain physiological and pathophysiological conditions.



## I. GENERAL INTRODUCTION

### A. The Concept of Necroinflammation

In this review, we discuss the cell death pathways (Origin) and different classes of DAMPs (Consequences) of necroinflammation. We define necroinflammation as the immune response to necrosis in a living organism. Necrosis is executed as a regulated process through defined signaling pathways such as necroptosis, ferroptosis, and pyroptosis or may happen in a nonregulated fashion as traumatic necrosis **(FIGURE 1)**. Whenever a cell undergoes necrosis, its intracellular content is released as damage associated molecular patterns (DAMPs). As a consequence of necrosis, DAMPs bind to different molecules on various other cells in the interstitium. Here, we provide a classification of DAMPs which is suggested in **TABLE 1**. As a mechanistic basis for this classification, we recommend the DAMP sensing as a differentiation criterion. With our increasing understanding of the distinct signaling pathways of regulated necrosis, a growing body of evidence suggests that RN pathways trigger different immune responses. Therefore, a given RN pathway may specifically fine tune the immune response for specifc needs to regenerate a given tissue or to fight given microbes more effectively. Differences in necroinflammation may therefore explain why several distinct cell death pathways are conserverd in our genome.

### B. General Introduction to Regulated Necrosis

Necrosis generally does not occur in an uncontrolled manner, at least not in nontraumatic diseases. Instead, it follows genetically determined signaling pathways. The cell death

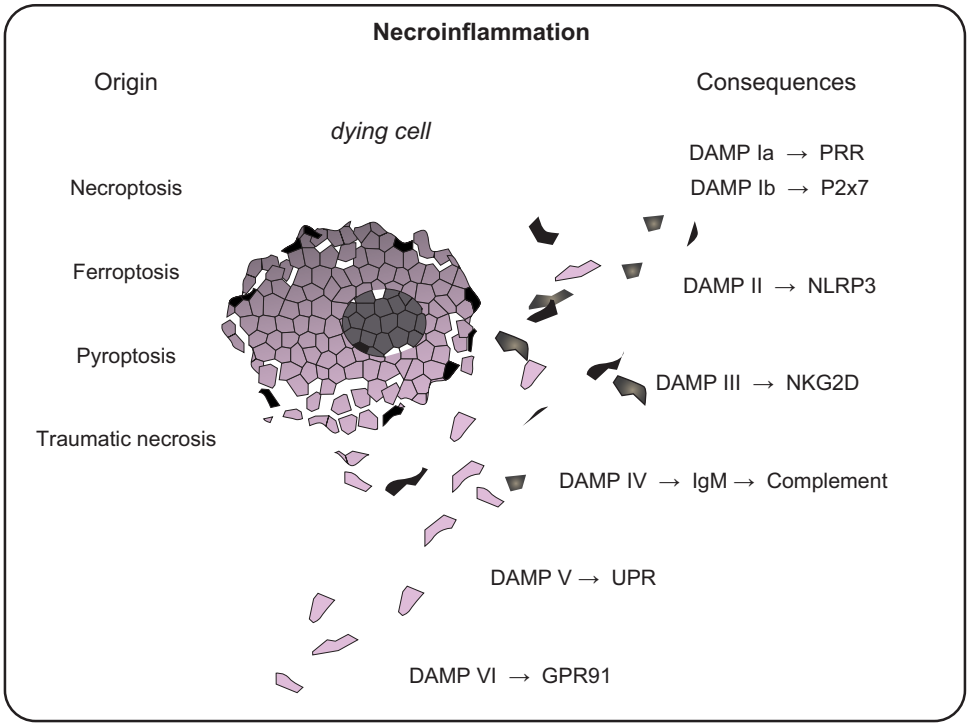



**FIGURE 1.** Origin and consequences of necroinflammation. Necrosis is executed as a regulated process through defined signaling pathways such as necroptosis, ferroptosis, and pyroptosis or may happen in a nonregulated fashion as traumatic necrosis. Whenever a cell undergoes necrosis, its intracellular content is released as damage-associated molecular patterns (DAMPs). As a consequence of necrosis, DAMPs bind to different molecules on various other cells in the interstitium. For a classification of DAMPs which is suggested in **TABLE 1** of this review, we recommend the DAMP sensing as a means of classifying DAMPs. In this review, we will discuss the cell death pathways (Origin) and different classes of DAMPs (Consequences) of necroinflammation. We define necroinflammation as the immune response to necrosis in a living organism.

community has been addressing the question of uncontrolled cell death for decades, thereby uncovering the molecular pathways of regulated necrosis (RN). Many RN pathways have been described, and it is a major task to unravel the overlapping and indistinguishable features of these pathways. This problem required some consensus on the definitions used that have been summarized in the Guidelines of the Nomenclature Committee on Cell Death, the most current version of which being in line with this review (181).

Necrosis, defined by plasma membrane rupture (PM-rupture), inevitably results in death of a particular cell. At this point the cell is dead by definition. As a consequence of PM-rupture, the intracellular content gains access to the interstitial space, to other cells, matrix components etc. The accessibility of surveillance immune cells to mitochondria, lysosomes, peroxisomes, and other organelles suggests that necrosis per se is a very immunogenic event. Intravital microscopy has visualized the process of necrosis in vivo (384), and DAMPs released during this process were in some cases referred to as cell death associated molecular patterns (CDAMPs) (330). The amount of DAMPs released by a cell is probably much more immunogenic when compared with a single molecule on the surface of a living cell, e.g., the incompatibility of single proteins such as HLA-mismatches and blood group antigens in the setting of transplantation.

It is of interest to realize that the process of regulated death takes some time. During this process, cells metabolize plenty of ATP to drive transcription of hundreds of molecules, including pro- and anti-inflammatory cytokines. Proteases are very active in some necrotic type cell death subroutines and process long-lasting cytokines, such as Pro-interleukin (IL)-1$\beta$ and Pro-IL-18 in case of pyroptosis. When such cells, often macrophages, finally undergo pyroptosis, the immunogenicity is not limited to the standard cytosolic arsenal of DAMPs, but contains some additional cytokines that enhance the immunogenicity beyond the level of default DAMP release. In contrast, active transcription of IL-33 during necroptosis stabilizes regulatory T cells in the surrounding microenvironment and thereby functionally dampens the immune response (540, 570). Analyzing these factors for each cell death subroutine, we will introduce a hierarchy for immunogenicity of necrotic cell death pathways in this review. It is because of the immunogenicity of regulated necrosis that we should understand these pathways and interfere with them therapeutically as indirect, but putatively highly potent immunosuppression.

## C. General Introduction to DAMPs

### 1. The danger/injury model in immunology

More than 20 yr ago, in January and April 1994, the danger hypothesis was first published proposing that a discrimination of the immune system between self and non-self does not sufficiently explain immune reponses. Its evolutionarily determined driving force was proposed to become alarmed and to react by any form of cell stress and/or tissue damage including allograft injury. Two major considerations led to

**Table 1.** *Classification of DAMPs involved in inflammation, adaptive immunity, and nociception*

| Classes of DAMPs* | Categories of Cognate Recognition Receptors/Sensors (Cell Bound, Humoral) |
|---|---|
| Class Ia DAMPs = DAMPs such as HMGB1, HSPs, nucleic acids including mitochondrial and cytosolic DNA | Sensed via binding to "classical" recognition receptors (= PRRs such as TLRs, RLRs, ALRs) on/in innate immune cells such as phagocytes including DCs, thereby triggering signaling pathways |
| Class Ib DAMPs = DAMPs such as CALR and eATP | Recognized by "nonclassical" recognition receptors such as the scavenger receptor CD91 and the purinergic receptors P2X7 thereby contributing to phagocytes including DCs activation |
| Class II DAMPs = DAMPs (e.g., eATP, uric acid) operating as second signals to activate the NLRP3 inflammasome | Sensed by NLRP3 receptor to form assembly of the NLRP3 inflammasome contributing to phagocytes including DCs activation |
| Class III DAMPs = DAMPs exposed on stressed cells such as MICs and ULBPs | Recognized by the activating NKG2D receptor, e.g., on NK cells thereby contributing to NK cell activation |
| Class IV DAMPs = DAMPs in terms of neoantigens/neoepitopes (such as NMHC-II, oxidized phospholipids, actin cytoskeleton, etc.) | Recognized by binding to preexisting natural IgM antibodies to activate the complement cascade thereby contributing to inflammation |
| Class V DAMPs = dyshomeostasis-associated molecular patterns (such as accumulation of unfolded proteins in the ER; intracellular ion perturbations, hypoxia, redox imbalance; etc.) | Sensed by sensors of the UPR (e.g., PERK) or sensed by NLRP3 receptor thereby contributing to inflammation and DC activation |
| Class VI DAMPs = metabolic DAMPs (such as succinate) | Recognized by the "nonclassical" recognition receptor GPR91 thereby promoting inflammation |
| Class VII DAMPs† = nociceptor-activating DAMPs (such as osmotic challenges, low and high temperature, capsaicin) | Sensed by nociceptors such as TRPA1 channels and TRPV1 |

*The attempt to classify DAMPs as depicted in this table is restricted for this article only and with focus on their crucial role in allograft rejection. †Class VII DAMPs sensed by nociceptors have been tentatively included in this table to show that DAMP-induced responses of the innate immune defense system may exceed the traditional phenomena of inflammation and adaptive immunity. Of course, this approach is debatable and we freely admit that there are still some deficits in our classification waiting for a final resolution. CD, cluster of differentiation; DAMPs, damage-associated molecular patterns; DCs dendritic cells; eATP, extracellular ATP; GPR91, G protein-coupled receptor 91; HMGB1, high mobility group box 1; IgM, immunoglobulin M; MICs, MHC class I chain-related proteins; NK, natural killer; NKG2D, natural killer group 2 member D; NLRP3, NLR family, pyrin domain-containing protein 3; NMHC-II, nonmuscle myosin II-A heavy chain; PERK, the protein kinase R (PKR)-like endoplasmic reticulum kinase; PRRs, pattern recognition receptors; P2X7, purinergic receptor P2X7; RLRs, retinoic acid-inducible gene (RIG)-I-like receptors; TLR, Toll-like receptor; TRPA1, transient receptor potential cation channel subfamily A member 1; TRPV1, transient receptor potential vanilloid subtype 1; ULBPs, UL16 binding proteins.

the development of this hypothesis: *1*) clinical trials with patients that received a renal allograft led to the conclusion that allograft injury inevitably resulted in a potent immune response in humans (338), and *2*) Polly Matzinger (428) suggested the conclusion that the "self/non-self" theory is inappropriate based on theoretical considerations. During the upcoming decades, further modification of this model by the two groups led to a more sophisticated outline of this hypothesis. This was triggered in particular by the developments and achievements published in the emerging field of innate immunity. Today, most scientists agree that tissue injury and metabolic changes in any tissue injury activate the innate immune system. The response may provide a broad range of protection including killing of invading pathogens, removing dead cells and cellular debris, but also balancing metabolic or psychological irregularities. Importantly, this response is thought to promote regenerative repair of destroyed tissues. Finally, when dangerous cell stress/tissue injury is associated with the presence of "non-self" or "altered-self" antigens (or even "self"), this unique defense system sends an SOS by inducing a supportive immune response.

How can the danger hypothesis be explained on a molecular level? In the early 2000s, the term *damage associated molecular patterns* (DAMPs) was first used (336, 578) This allowed the understanding of "danger signals" as defined molecules. In the 2003 article, Land (336) wrote: "Damage-associated molecular patterns ('DAMPs') such as heat shock proteins, arising in the stressed allograft, serve as endogenous ligands for and interact with Toll-like receptors (TLRs) on cells of the innate immune system such as donor- or recipient-derived dendritic cells and donor-derived vascular cells and, by this engagement, activate them." In the 2004 article, Seong and Matzinger (578) wrote: "It is currently thought that immune responses are initiated by pathogen-associated molecular patterns or by tissue-derived danger/alarm signals. . . . Many of them might be part of an evolutionarily ancient alert system in which the hydrophobic portions

of biological molecules act, when exposed, as universal damage-associated molecular patterns to initiate repair, remodeling and immunity."

In fact, the very first clue of the existence of such molecules was provided by studies published already in 2000/2002 by Shi et al. (587) and Shi and Rock (586). These authors demonstrated that tumor cell death may provide a trigger for the stimulation of T cells. Thereafter, in 2003, uric acid was first ascribed a role as a danger signal (585), which was later broadly accepted as first non-bacterial DAMP (85).

### 2. About DAMPs, PAMPs, and MAMPs

As originally defined, danger signaling DAMPs are endogenous molecules, that is, encoded by the host's endogenous genome. As constitutive DAMPs, they are ad hoc, that is, immediately released under certain conditions of major cell stress or tissue injury and do not require protein synthesis. Constitutive DAMPs may activate cells of the innate immune system by operating, extra- or intracellularly, as preexisting molecules, aggregated molecules, fragments of molecules (e.g., hyaluronan fragments), or intracellularly dislocated molecules (e.g., presence of nuclear DNA in the cytosol).

As previously suggested for pathogen-associated molecular patterns (PAMPs), DAMPs may be sensed by Toll-like receptors (TLRs), the prototype pattern recognition receptors (PRRs). It is also possible that DAMPs are recognized through stimulation of "nonclassical" receptors such as scavenger receptors. These are found in the plasma membrane or within intracellular compartments of innate immune system. Accordingly, DAMPs are either *1*) dislocated molecules inside of a challenged cell, *2*) sorted to the cellular surface of stressed cells, *3*) secreted during the early progress of regulated necrosis (see below for details), *4*) released upon plasma membrane rupture, or *5*) shed from the affected extracellular matrix (ECM) (50, 348, 391, 551, 568). Importantly, constitutive DAMPs also include "homeostatic danger signals," denoted here as dyshomeostatic–associated molecular patterns to preserve the acronym "DAMPs." These DAMPs reflect and are associated with molecular perturbations of tissue homeostasis, such as pH shifts, redox imbalance, intracellular ion perturbations, and specific signaling pathways of regulated necrosis. Intrinsic DAMPs may intracellularly signal dangerous pathological stress (179).

From constitutive DAMPs, inducible DAMPs may be distinguished which can be regarded as molecules "newly made" during ongoing transcriptional activities, for example, in cells undergoing regulated cell death. DAMP-induced secretion of type I interferons (IFN) may be regarded as an example of inducible DAMPs, that is, DAMPs which may amplify (or even restrict) the immunogenicity of a dying cell.

Another difficulty to exactly define danger signaling molecules refers to the inclusion of so-called exogenous DAMPs. For example, a clear distinction of DAMPs from PAMPs is difficult to make. PAMPs in terms of pathogen-associated molecular patterns were originally defined as exogenous molecules derived from microbes to activate PRR-bearing innate immune cells, thereby providing the immune system with the critical distinction between self and non-self (431). On the other hand, lipopolysaccharide (LPS), a prototypic PAMP, is an active component of cigarette smoke, thereby acting as an exogenous DAMP (230). Likewise, allergens, at least in a wider sense, are also regarded as exogenous DAMPs able to instigate allergic diseases via recognition by PRRs such as TLRs (455, 597). However, one has to differentiate here. Some allergens such as pollen diffusates, for example, from *Olea europaea*, possess proteases that can damage epithelial tight junction proteins thereby activating the innate immune system (656). Some other allergens such as the house dust mite allergen *Dermatophagoides pteronyssinus group 2* (Der p 2) indirectly activate the innate immune system via interaction with the TLR4 signaling complex by mimicking MD-2, an adapter protein of TLR4 (46). Again some other allergens such as *Fel d 1* from cat dander associate with TLR4 via binding to one of its ligands (239). Yet, in contrast to those indirect modalities of innate immune activation, the metal allergens nickel, cobalt, and recently also palladium act as true bona fide exogenous DAMPs by triggering innate immune activation via direct stimulation of TLR4 signaling (528, 531).

The definition of DAMPs is not trivial because of the plethora of different structures that are released. Additional complexity is added by their role in pathogen-induced inflammation, generally believed to be exclusively caused by PAMPs. Evidence accumulates for DAMPs to represent essential triggers during immunity against invading microbes, not limited to bacteria, but also including viruses (104, 225, 279, 406, 559, 637). Recent data support this hypothesis. In the mammalian gut, the innate immune system may be responsive only to pathogenic bacteria, but to spare the commensals (281, 497, 619). As a reponse to this observation, it has been required to classify microbe-associated molecular patterns (MAMPs) as a separate term. However, the molecular basis for the recognition of commensals and their associated tolerance remains to be investigated. One possible explanation is the sensing of pathogen-induced DAMPs instead of exclusively surveilling for MAMPs. Accordingly, at least for the in vivo scenarios, we here propose for reasons of precision the equation: exogenous MAMPs + endogenous DAMPs = operating as PAMPs or (as valid for some bona fide innate immune response-promoting molecules such as LPS) PAMPs = DAMPs.

In this article, we will focus on endogenous DAMPs of (mainly) constitutive and inducible origin only. In regard to the generation of inducible DAMPs, we will discuss the time

period between the decision of a cell to undergo a certain type of regulated necrosis and the burst of the plasma membrane. Characterized by active production of pro- or anti-inflammatory cytokines, this period can be regarded as a window of opportunity where a dying cell can shape/direct its immunogenicity via generation of inducible DAMPs in adjunction to the release of constitutive DAMPs during final death associated with complete plasma membrane rupture.

### 3. Role of DAMPs in human diseases

There is increasing evidence from clinical observations and trials that DAMPs play a crucial role in the pathogenesis of human diseases (346, 347). It is beyond the scope of this review to list the data on DAMPs in each particular disorder, but we will refer to immunologic and cardiovascular diseases as examples that may help to understand the general nature of DAMPs and necroinflammation. In general, DAMPs are of importance to human diseases whenever necrotic cell death is involved.

With respect to allorecognition upon solid organ transplantation, the danger hypothesis was first mentioned in the early 2000s (335–337, 340, 341, 351). A growing body of literature suggests that allograft injury results in DAMP release (2, 116, 124, 148, 159, 247, 343, 345, 384, 460, 499, 513, 652, 692, 729). This may be of particular importance for the "canonical" (oxidative) injury that has been demonstrated to be inevitably associated with donor brain death and during ischemia-reperfusion injury. It is unclear, however, to which extent this immune response may contribute to acute or chronic (antibody-mediated) rejection. Recipient-derived monocytes and dendritic cells (DCs) rapidly invade the graft following the process of transplantation and may respond to the mass of DAMPs in an allograft by eliciting a robust adaptive immune respone. Donor specific antibodies (DSA) and panel reactive antibodies (PRR) may originate from the very early phase after transplantation through this mechanism. Consequently, DAMPs may result in all forms of allograft rejection, providing a prototype example for the current concept of necroinflammation (2, 116, 124, 148, 159, 247, 343, 345, 384, 460, 499, 513, 652, 692, 729).

A role of DAMPs is also being discussed in cardiovascular diseases (215). For example, in atherogenesis, vascular injury-induced DAMPs, via activation of smooth muscle cells, vascular macrophages, and DCs, orchestrate a network of processes including vascular inflammation, intima fibrosis, and autoimmune responses leading to atherosclerosis (345). In addition, myocardial infarction as a complication of atherosclerosis provokes an intense reperfusion injury-induced inflammatory response. Functionally, left ventricular remodeling, diminished left ventricular ejection fraction, and heart failure (646c) may follow. Necroinflammation, therefore, may provide a concept of the recently identified observations in preconditioning, e.g., during cardiac surgery (232, 437).

Necroinflammation may also explain diseases in critically ill patients. During hypoxia, ischemia, trauma, surgery, and critical infections, DAMP release is the molecular driver of systemic hyperinflammatory syndrome such as systemic inflammatory response syndrome (SIRS) (610, 629). Accordingly, the use of DAMPs as biomarkers or therapeutic targets in intensive care patients is meanwhile highly appreciated and will certainly contribute to improve the outcome of these acute life-threatening diseases in the near future.

Moreover, there is also an emerging role for DAMPs in metabolic diseases based on a strong link between inflammation and metabolic dysfunction. DAMPs such as the high mobility group box 1 (HMGB1), extracellular adenosine triphosphate (eATP), and nucleic acids were described to be involved in the inflammatory response in metabolic disorders including, but not limited to, diabetes, gout, obesity, and metabolic syndrome (185). For example, type 1 diabetes mellitus involves DAMP-induced autoimmunity. This process may result in dysfunction and destruction of $\beta$-cells. Notably, stress of the endoplasmic reticulum (ER) reflecting the presence of "homeostatic" DAMPs, as induced, for example, by accumulation of prolonged hyperglycemia-induced (misfolded/unfolded) pro-insulin, results in the unfolded protein response (UPR) that is suggested to contribute to the inflammatory downfall of $\beta$-cells observed in patients with type 1 diabetes mellitus (150, 438, 590, 685). Along similar lines, DAMPs have been found to play a crucial role in several autoimmune diseases, the development of which is caused by both genetic predispositions and environmental factors (238, 405, 490). For example, as reviewed in Reference 346, in regard to the pathogenesis of systemic lupus erythematosus (SLE), accumulating evidence suggests oxidative stress-related cellular injury (ferroptosis, see below) to be of central importance. This autoimmune disorder results in a failure to remove necrotic debris and thereby in a persistent activation of the immune system. During this process, it is tempting to speculate that antibodies against dsDNA may emerge. Importantly, necrosis-associated novel autoantigens may function as DAMPs, cytosolic self-RNA, and self-dsDNA (323, 405, 406, 514, 569). SLE-associated DAMPs may subsequently trigger DCs which ignite adaptive immune responses (310). In addition, as shown by more recent studies, inadequate removal of cellular remnants in the germinal centers of secondary lymphoid organs may result in the presentation of autoantigens by follicular DCs to autoreactive B cells that had been generated by chance during the process of somatic hypermutation, a process leading to loss of peripheral tolerance (407, 514).

Furthermore, a role of DAMPs is being discussed in neurodegenerative diseases (628). For example, in Alzheimer dis-

ease, following primary neuroinflammation (caused by still unknown injurious agents), β-amyloid, S100 proteins, and HMGB1 are regarded as secondary key DAMPs that further exacerbate production of proinflammatory cytokines, thereby contributing to disease progression (102). The release of proinflammatory cytokines in neurodegeneration may well be associated with regulated necrosis, as recently demonstrated for amyotrophic lateral sclerosis (256).

Most importantly, modern developments in oncoimmunology regarding mechanisms of immunosurveillance and elimination of cancer cells are also based on the danger/injury model. In fact, increasing evidence from oncoimmunological research work during the last decade has shown that, in analogy to DAMP-induced pathways leading to alloimmunity/allograft rejection, distinct DAMP-induced pathways, evoked in the course of "immunogenic cell death" (ICD) in terms of a peculiar instance of regulated cell death (RCD) of tumor cells, can also result in antitumor immunity/tumor rejection (189, 321, 336, 338, 428, 578, 585, 621, 752), probably with an outstanding role for RN (646a) rather than apoptosis (see below).

Here, we will comprehensively summarize and attempt to provisionally classify DAMPs. Subsequently, RN pathways as sources of DAMP emission will be highlighted. Finally, we will discuss evidence for the role of DAMPs and RN in both allograft and tumor rejection which reflect similar injury-initiated, DAMP-induced, innate/adaptive immune-mediated scenarios of fundamental type.

## II. REGULATED NECROSIS

### A. Why Do We Evolutionary Conserve Pathways of Regulated Necrosis

For the cell itself, it does not matter how it dies. However, it does matter for its environment. Most likely, the reason for the genetic conservation of several subroutines of regulated necrosis is the difference in immunogenicity to certain parts of the innate and/or adaptive immune system as a response to different challenges that the organism persistently conflicts with because of microbes. The delay between the decision to undergo a certain type of regulated necrosis and the burst of the plasma membrane provides an important window of time for these cells to actively produce or mature pro- or anti-inflammatory cytokines that may direct the strong inflammatory response to the DAMPs released into a more or less systemic inflammation. This window is just as narrow as it has to be to prevent viral or bacterial expansion. Upon massive necrosis, as it happens during ischemic damage of an organ, however, cytokines and chemokines, compared with the release of intracellular organelles including peroxisomes, lysosomes, nuclei, and mitochondria, can only be of comparably minor importance, and it would be entirely wrong to assume that there is an anti-inflammatory form of regulated necrosis. In the following, we will introduce the three major pathways of regulated necrosis, namely, necroptosis, ferroptosis, and pyroptosis.

### B. Necroptosis

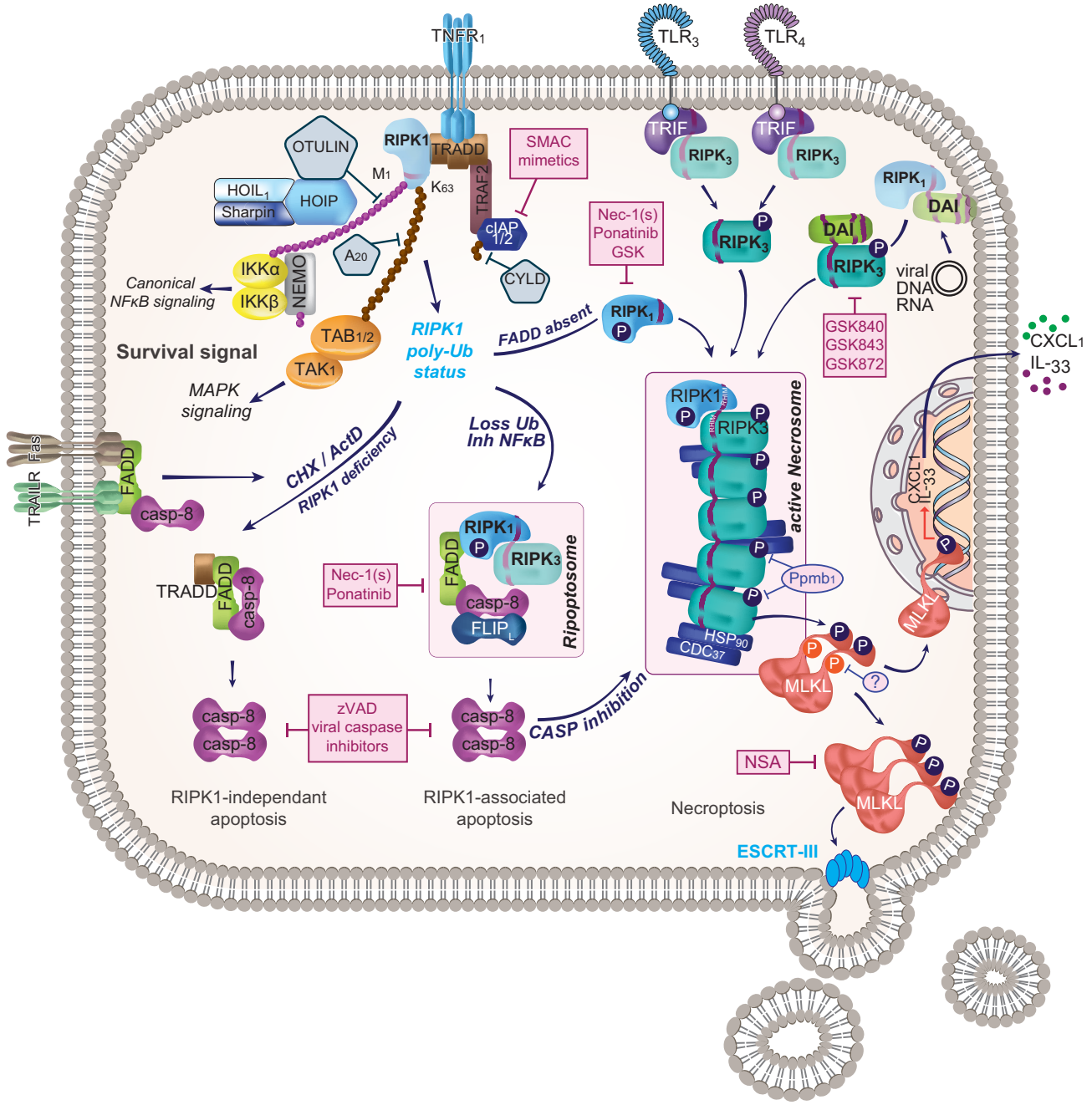
Among the pathways of regulated necrosis, necroptosis represents by far the best-studied RN subroutine, and translational medicine on necroptosis prevention (380, 383) has already reached phase 2 clinical trials (227). Necroptosis is distinct from other forms of regulated necrosis because it requires phosphorylation of the pseudokinase mixed linage kinase domain like (MLKL). The only known kinase to phosphorylate MLKL is receptor-interacting protein kinase 3 (RIPK3). All details of our current understanding of the necroptosis pathways can not possibly be listed here, so the introduction to necroptosis is biased to what we consider the most important facts to understand necroptosis as the origin of necroinflammation (386, 462). **FIGURE 2** provides a simplified and general overview of the signaling pathway of necroptosis.

#### *1. The signaling pathway of necroptosis*

The necroptosis signaling pathway is controlled predominantly by kinases and E3 ligases. Death receptor-mediated activation of MLKL, the essential and defining mediator of necroptosis (607), requires both of these signals: phosphorylation and loss of polyubiquitination.

The default signal of TNFR1 results in the polyubiquitination of receptor-interacting protein kinase 1 (RIPK1), RIPK1-dependent and RIPK1-independent NF-κB activation (135, 690), expression of cellular FLICE-inhibitory protein (cFLIP), and resistance to cell death (320). The RIPK1-precipitating complex formed in this scenario has been referred to as complex 1 and is reviewed in detail elsewhere (45, 303, 492, 495, 646a, 680). Upon deubiquitination of RIPK1 (see below for details), pro-caspase-8 may be recruited to this complex via a death domain (DD) that binds the DD of Fas-associated protein with death domain (FADD), resulting in forced proximity of pro-caspase-8 and activation by proteolytic cleavage of the caspases to form a functional caspase-8 homodimer capable of cleaving effector caspases, such as caspase-3, caspase-6, and caspase-7 to mediate and execute apoptosis (320). Importantly, however, instead of forming homodimers, caspase-8 favors the dimerization with the long version of cFLIP to assemble a cFLIP/caspase-8 heterodimer (493, 494). This heterodimer, by incompletely understood means, but including RIPK1, RIPK3, and CYLD cleavage, inactivates RIPK3, the key kinase in the necroptotic pathway. The inhibitory effect of the cFLIP/caspase-8 heterodimer on necroptosis explains why caspase-8-deficient mice are embryonically lethal, and therefore explains the

reversal of the lethal caspase-8-ko phenotype on a RIPK3-deficient background in mice (276, 493). Consequently, the loss of either cFLIP or caspase-8, or the inhibition of this complex by virally expressed or synthetic caspase inhibitors, unleashes the activation of RIPK3 upon RIPK1-mediated phosphorylation (126, 127). Until today, RIPK3 is the only identified kinase capable of phosphorylating MLKL and the only kinase that mediates necroptosis downstream of RIPK1 (95, 235, 730). However, RIPK3 signaling may also result in necroptosis-independent signaling (9, 471, 481). Both RIPK1 and RIPK3 contain a rip homotypic interacting motif (RHIM) domain which is typical of the necroptosis pathway (277, 278). Upon caspase-inhibiting conditions, it is believed that deubiquitinated RIPK1 can no longer intercalate its RHIM domains between the RIPK3-RHIMs and therefore RIPK3 auto-oligomerizes to form a higher order structure referred to as the necrosome, a scenario that might explain the lethal phenotype of RIPK1-deficient mice and the viability of the RIPK1-kinase dead knock-in mice (127, 273, 480, 541). RIPK3 in the necrosome is present in a phosphorylated manner, and it is not entirely clear to which extent this phosphorylation is mediated by RIPK1 or RIPK3 itself. However, the necrosome is stabilized by HSP-90 and CDC-37, two chaperones that are required for the fully active necrosome (364, 365). The RHIM domain of RIPK1 controls necrosome formation by



direct engagement of the DNA-sensing molecule DAI which for itself contains two RHIM domains (277, 275, 453, 622, 644). One of these RHIM-domains appears to exert anti-necroptotic activity as it keeps the other DAI-RHIM domain in check. Upon loss of the RIPK1-RHIM, necroptosis-mediated DAMP release and subsequent inflammation in vivo is mediated through DAI also referred to as Z-DNA binding protein 1 (ZBP1) (376, 482).

An active necrosome structure is required to phosphorylate the activation loop of the pseudokinase MLKL which exposes a four helical bundle (4-HB) upon *1*) phosphorylation by RIPK3 in its activation loop and *2*) the dephosphorylation of a persistent phosphate residue in the hinge region between the 4-HB and the default protein (465, 466, 546). Once pMLKL is fully active, it was demonstrated to oligomerize and bind to phosphatidylinositol-4,5-bisphosphate ($PIP_2$) in the plasma membrane (134, 669). It has been proposed that pMLKL forms pores in the plasma membrane to mediate plasma membrane rupture (669), but this remains to be demonstrated in cells or in vivo. In fact, recent data indicate that necroptosis regulates membrane repair mechanisms by means of the endosomal sorting complexes required for transport (ESCRT) machinery downstream of pMLKL (213). In contrast, the absence of ESCRT component results in MLKL-dependent necroptosis, indicating a complex network of membrane interactions downstream of pMLKL (213). Obviously, in that scenario, phosphorylation of the activation loop of MLKL is not sufficient to mediate necroptosis (213, 716, 728). At least two independent groups reported that vesicles are shed from the surface of necroptotically dying cells (213, 728). This ESCRT-dependent mechanism extends the time to plasma membrane rupture (213). However, the precise execution mechanism of necroptosis may be arranged; we do understand necroptosis as a signaling pathway to defend against microbes, especially viruses that express caspase inhibitors (235, 486).

It is beyond the scope of this review to introduce necrosome formation downstream of the activation of Toll-like receptors that engage the RHIM-containing protein TRIF and the signaling of DAI (235, 274, 275, 277), that have been reviewed elsewhere (55, 56, 278) and are currently under extensive investigation.

### *2. Control of necroptosis by posttranslational modification*

The paramount decision downstream of TNFR1 signaling is to either signal survival via complex 1, nonimmunogenic apoptosis via effector caspases or immunogenic necroptosis via RIPK3-mediated phosphorylation of MLKL. Only the latter is associated with the release of DAMPs (see below). The most important molecule that navigates this life-and-death decision is RIPK1, more precisely the polyubiquitination status of RIPK1. It has been nicely demonstrated that both linear and K63 polyubiquitin chains are present in RIPK1 in unstimulated cells, and that the loss of both of these systems results in activation of cell death pathways. In particular, linear ub-chains (M1) are controlled by the linear ubiquitin chain assembly complex (LUBAC) which consists of the proteins SHARPIN, HOIL1, and HOIP. This complex is antagonized by the deubiquitinase OTULIN which removes M1-polyUb linkages (114, 168, 245, 305). OTULIN deficiency or dysfunction results in autoimmunity, rendering OTULIN an essential negative regulator of inflammation and clearly demonstrating the importance of this system in the concept of necroinflammation (114). K63 linkages are controlled by cellular inhibitors of apoptosis (cIAPs) in balance with deubiquitination enzymes such as CYLD (which also antagonizes M1-linkages) and A20 (133, 222, 498). A20 and cIAP1 have been identified as a negative regulators of necroptosis in the early days, and these observation deserve special credit because they paved

**FIGURE 2.** The signaling pathway of necroptosis. Necroptosis is defined as regulated necrosis, mediated by the molecule MLKL. Phosphorylation of MLKL in the activation loop (blue phospho site in this figure) results in exposure of the 4-helical bundle (4-HB) of MLKL which allows binding with $PIP_2$ in cellular membranes including the plasma membrane and subsequent plasma membrane rupture that is regulated downstream of pMLKL by the ESCRT complex. In parallel, pMLKL (phospho-MLKL) translocates to the nucleaus and results in the active transcription of CXCL1 and IL-33. The concise mechanisms of plasma membrane rupture have yet to be defined. NSA (necrosulfonamide) inhibits pMLKL function and necroptosis in human cells. Removal of a specific phosphate (red in this figure) in the hinge region between the 4-HB and the activation loop of MLKL is required for pMLKL to function as a necroptosis inducer, but the phosphatase required for this process has not been identified. The only known kinase that phosphorylates MLKL is receptor-interacting protein kinase 3 (RIPK3). Oligomerization of RIPK3 molecules through their rip homotypic interacting motif (RHIM domain, purple line in the molecules RIPK1, RIPK3, TRIF, and DAI) results in an amyloid-like structure referred to as the necrosome, which is stabilized by CDC37 and HSP90. Engagement of the necrosome can be a consequence of TLR-signaling through TRIF/RIPK3, DAI/RIPK3, and RIPK1/RIPK3. The best defined "default" necroptosis pathway through death receptors such as TNFR1 requires *1*) loss of linear (M1) and K63 polyubiquitin chains from RIPK1 and *2*) the inactivation of caspases, or the inability to engage caspases, e.g., by loss of FADD. Other than the necrosome, the ripoptosome additionally contains FLIPlong and FADD and therefore is capable of signaling apoptosis, unless caspases are inhibited by either viruses or synthetic caspase-inhibitors such as zVAD. Upon maintainance of the polyubiquitin chains on RIPK1, TNFR1 signaling results in robust activation of canonical NF−κB signaling and TAK1-mediated MAPK-signaling. These events result in a pro-survival signal. In this scenario, linear-ub chains on RIPK1 are controlled by the linear ubiquitin chain assembly complex (LUBAC), counteracted by the deubiquitinase (DUB) OTULIN. cIAP1/2 are recruited to the TNFR1 complex by TRAF2, required for the K63 linkages on RIPK1. cIAP1/2 themselves become polyubiquitinated to function properly, and this signal is opposed by the DUBs CYLD and A20. Fas and TRAILR, two TNFR-superfamily members, are depicted to demonstrate the standard pathway of apoptosis in this context. Specific inhibitors of critical enzymes in this pathway are indicated in purple.

the way for polyubiquitin-research in necroinflammation (647, 648).

### 3. Necrostatins and the in vivo role of necroptosis

Necroptosis has attracted tremendous attention because it appeared to be the solution for necrosis in general, probably the most widespread unmet clinical need in modern medicine. In fact, necrosis occurs during transplantation, stroke, myocardial infarction, sepsis, trauma, cancer, pancreatitis, macular degeneration, and hundreds of other pathologies. But the dream to prevent necrosis in all of these disorders has quickly lost its illusion when it became obvious that prevention of necroptosis by either RIPK1-kinase inhibitors or in vivo models of RIPK3-deficient mice provides only partial protection from necrosis, if any.

With all the published papers on protective effects in some in vivo models, three facts need to be kept in mind when it comes to interpretation of these data. First, the original compound necrostatin-1 (Nec-1) (120), a small molecule and a hydantoin (119, 122), has been demonstrated to function as a ferrostatin (see below) with intrinsic antinecroptotic activity (176). In several in vivo models, protective effects by Nec-1, therefore, may be because of ferroptosis prevention rather than a role in necroptosis. Second, RIPK3-deficient mice have been investigated in a broad fashion, but as we understand today, RIPK3, as to the nature of its kinase, exerts several effects beyond phosphorylation of MLKL, including direct effects on inflammation (9, 471, 481). Finally, the existence of other RN-pathways demands to identify the relative contribution of each of the RN-pathways in a given model of necrotic disease. In fact, employing combination therapies that target diverse RN-pathways at the same time provide much stronger beneficial effects (381, 385).

However, RIPK3-deficient mice are protected to a significant extent from ischemia reperfusion injury (IRI) in the heart (480) and the kidney (381). In addition, RIPK3-ko mice are slightly less sensitive to the tumor necrosis factor (TNF)-$\alpha$-mediated shock model (147, 382, 480), but still die following systemic inflammation (SIRS). Other published beneficial effects have either not been reproduced or have been nonreproducible. With respect to highly specific RIPK1-kinase inhibitors (121), such as Nec-1s, ponatinib (160, 472) and even more potent compounds, it appears that protection from SIRS rather than protection from ischemic injury predominates its beneficial effects. In our hands, Nec-1s and ponatinib did not provide any protection from IRI in the kidney (Linkermann et al., unpublished observation). However, because RIPK3-ko are protected from IRI and other models of ischemic injury (354, 381, 396, 480), one potential explanation for this virtual discrepancy may be induction of necrosis in a RIPK1-independent manner, e.g., through TLR signaling (275) or the intracellular protein Z-DNA binding protein 1 (ZBP-1, also referred to as DAI) (644), a protein that is actually inhibited by RIPK1 (376, 482).

## C. Ferroptosis

Ferroptosis is defined as an iron-dependent form of regulated necrosis that is mediated by lipid peroxidation, predominantly polyunsaturated fatty acids (PUFAs) (709). Therefore, ferroptosis is clearly distinct from other forms of cell death. Iron chelators such as desferoxamin (DFO) have been investigated in isolated renal tubules that underwent hypoxia/reoxygenation for decades, and the role of free iron has been extensively characterized (679, 723–725). Several studies were performed using DFO and other chelators for acute kidney injury (AKI) (461), the outcome of which was inhomogeneous. Some data obtained from pigs have recently demonstrated beneficial effects of DFO when standardized conditions may be provided (659). Importantly, however, the right dosing appears to be problematic, and several reports have suggested acute kidney injury after DFO overdose (33, 101). In addition, most of the clinical data rely on small, poorly controlled single center trials and therefore conclusions were naturally limited. The development of inhibitors of ferroptosis, ferrostatins, may therefore represent a promising novel therapeutic approach.

### 1. "Iron catalyzed regulated necrosis," the signaling pathway of ferroptosis

Being highly reactive, free intracellular iron is dangerous (291, 357), and bound to ferritin, the oxidative capacity of free iron and the amount of oxygen radicals is controlled. Heavy-chain ferritin was found to be protective in models of IRI (41), and the role of iron in acute kidney injury induced by cisplatin toxicity has been well established (477). Clearly, free catalytic iron represents a risk factor for acute kidney injury as nicely demonstrated in a series of 250 patient who underwent cardiac surgery (357). When the term *ferroptosis* was first ascribed to the process of iron-catalyzed regulated necrosis, iron chelation was demonstrated to prevent this deadly signal (130). Iron availability in general, but importantly also during ferroptosis, is controlled by phophorylase kinase G2 (PHKG2) (709). In ferroptosis, iron-dependent arachidonate lipoxygenase (ALOX)-mediated peroxidation of PUFAs and other membrane lipids such as phosphatidylethanolamine and $PIP_2$ (mainly expressed in the plasma membrane) and cardiolipin (CL, mainly expressed in the mitochondrial membranes), by unknown means results in loss of NADPH abundance and subsequent loss of plasma membrane integrity (176, 588, 633). Constitutive ALOX activation is antagonized by the phospholipid peroxidase and oxidoreductase glutathione peroxidase 4 (GPX4), a selenoprotein which employs glutathione (GSH) to reduce $H_2O_2$ to GSSG and $H_2O$. Indirectly, GPX4 thereby inhibits lipid peroxidation and ferroptosis, the loss of GPX4 results

in early embryonic lethality, and conditional inducible deletion of GPX4 from neurons or renal tubular cells later during life results in lethality as well (62, 107, 176, 218, 265, 715). NADPH is required for another enzyme, glutathione reductase, to recycle GSH from GSSG, and the action of this enzyme results in ~90% of glutathione to be present in its reduced form in most cells (22). Consequently, *1*) loss of intracellular GSH, *2*) pharmacological inhibition of GPX4, and *3*) loss of the GPX4 protein result in spontaneously occurring ferroptosis.

Besides recycling by the glutathione reductase, intracellular concentrations of GSH are maintained by activity of the GSH synthase which requires the substrates glutamine, cysteine, and glycine to function. A glutamate/cystine antiporter in the plasma membrane referred to as "system XC-minus" provides the cells with cystine which intracellularly is metabolized to cysteine, the rate-limiting amino acid for GSH synthesis (580). This antiporter consists of the two subunits SCL7A11 and SCL3A2. SCL7A11 is expressed under the control of the p53, and a connection between p53 and ferroptosis has therefore been suggested and has initiated an extensive scientific debate (31, 67, 180, 263, 352, 371, 626, 671, 700, 714). However, there are additional aspects to consider with respect to the p53-ferroptosis interaction. This connection appears to be likely relevant because the p53 gene is in close proximity to some ALOX genes, but the connection between iron, p53, and PHKG2 may be more complex than simply through genetic regulation (709). In cancers, p53 and lipoxygenases have been linked several years ago (296).

The activity of system XC-minus is compromised by the compound erastin which shifts the balance to less GSH production, less redox capacity of GPX4, and more lipid peroxidation, and therefore is one of the ferroptosis inducers (FINs). Alternatively, ferroptosis can be experimentally induced by the direct GPX4 inhibitor RSL3 and several other ferroptosis-inducing agents (588, 710). Importantly, as a characteristic sign of regulated cell death pathways, ferroptosis was demonstrated to be extensively metabolically regulated (589), and several proteins involved in ferroptosis have been detected in a human haploid-cell screen (131), but these proteins need to be investigated in more detail in several settings to understand their role in the ferroptosis pathway. More clearly, in a genetic approach, the deletion of the GPX4 gene locus results in lethality (62, 107, 715) and the conditional deletion of GPX4 from renal tubular cells resulted in tubular cell ferroptosis within 48 h following the inducible gene knockout which can experimentally be prevented by the addition of inhibitors of ferroptosis (ferrostatins). Perfusion of hand-picked renal tubules with erastin results in a synchronized necrotic change of renal tubular morphology which was termed synchronized necrosis and apparently explains the process of acute tubular necrosis (ATN), so-called "muddy brown casts," a clinical diagnostic criterion of acute kidney injury (AKI) (385). **FIGURE 3** was assembled as example of the currently identified key players in ferroptosis.

### *2. Ferrostatins*

Ferrostatins are the strongest small molecules for the prevention of IRI by a single compound (108, 385). No other compounds yielded a comparable level of protection from isolated renal tubules or in vivo in kidney and liver models. Originally found in a screen for inhibitors of erastin-induced ferroptosis in HT1080 cells, ferrostatin-1 (Fer-1) was identified (130), basically acting as a lipid antioxidant. Fer-1 is the most commonly used compound to study ferroptosis in cells, and therefore, it is of importance to mention that also the first described inhibitor of necroptosis, Nec-1, functions as an effective inhibitor of ferroptosis (176). In addition, the plasma half-life and the absorption in liver liposomes along with the plasma stability are far from optimal, and the statistically significant effects seen in in vivo models (385, 420) most likely underestimate the therapeutic preclinical potential of ferrostatins. Other than Fer-1, the compound 11–92 was much more effective in preventing tubular necrosis (595), and further developments of 16–86 in direct comparison with its inactive derivative 16–79 yielded strong effects in preclinical models of AKI. However, 16–86 is not stable in plasma over several hours, and further compounds are currently under development. Similarly, liproxstatin-1 was developed and investigated in a model of liver IRI with strong beneficial effects (176). One particularly tempting approach focuses on the development of a ferrostatin that contains intrinsic antinecroptosis activity. In theory, Nec-1 has demonstrated that this shall be possible!

### *3. Ferroptosis and cancer*

With respect to ferroptosis, there are several aspects to consider in cancer, especially in diffuse large B-cell lymphomas and renal clear cell carcinomas (710). First, p53 was demonstrated to directly inhibit the expression of the SCL7A11 subunit of the system XC-minus (67, 180, 263, 714). Importantly, p53 and the machinery of ferroptosis may also be interconnected on other levels, such as a transcriptional level. In this sense, the p53 encoding gene lies in direct proximity to several ALOX genes, possibly suggesting an overlapping regulation. Second, free iron is important in the regulation of cell death in cancer (467, 671), but processes such as nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy (selective autophagy of ferritin) clearly affect the fine tuning of intracellular free iron (413, 414). Interestingly, this process is dependent on iron-dependent proteolysis of the HERC2 ubiquitin ligase (413). Autophagy, in addition, is required for several tumors to survive, especially when p53 is mutated (706). It is therefore possible that the central necrosis in tumor metasta-

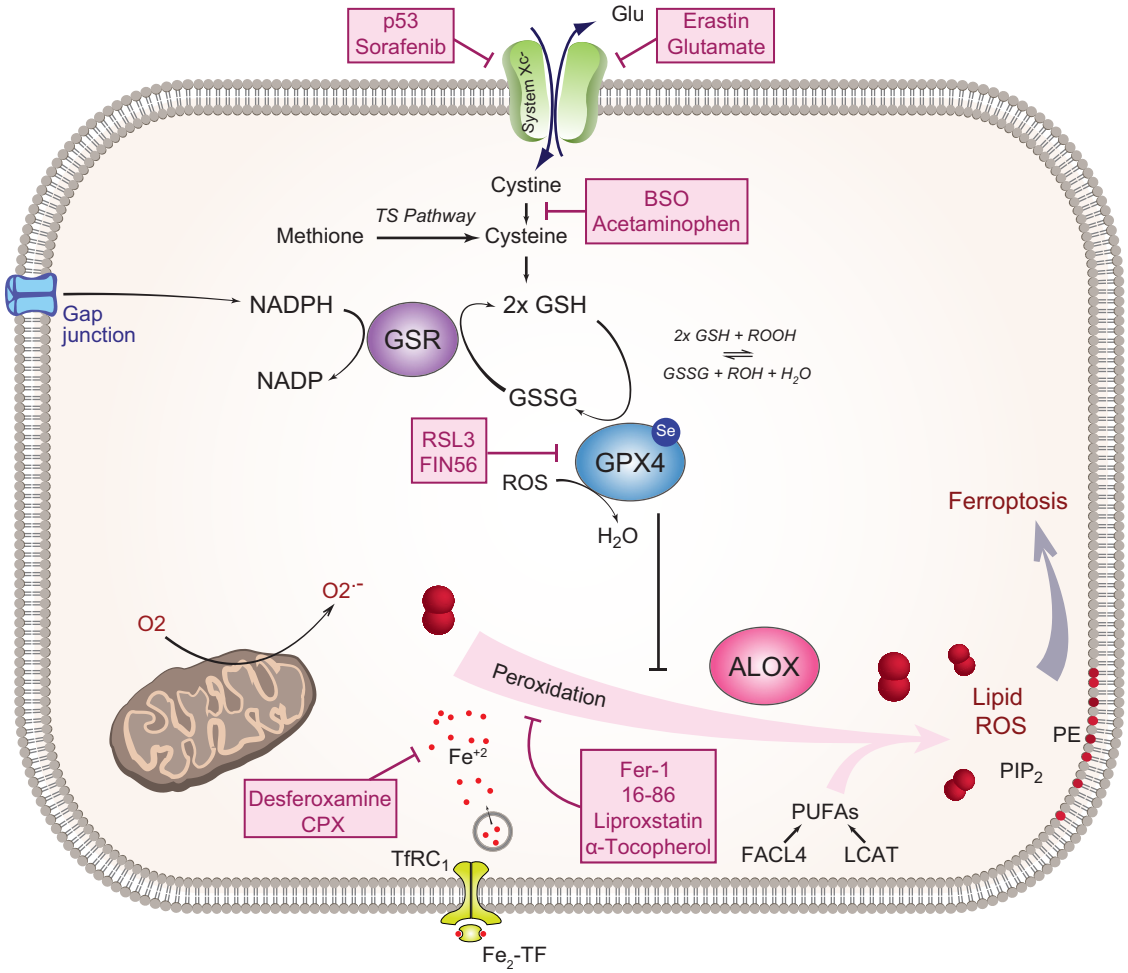



**FIGURE 3.** Iron catalyzed necrosis: the signaling pathway of ferroptosis. During ferroptosis, peroxidation of lipids such as phosphatidylethanolamine (PE) and $PIP_2$ results in plasma membrane rupture, but the precise mechanisms are elusive. Peroxidation of such lipids is largely mediated by lipoxygenases (ALOX) which are routinely inhibited by active glutathione (GSH) peroxidase 4 (GPX4). Peroxidation requires labile iron and therefore can be antagonized by iron chelators and modulated by all means that regulate the intracellular free iron pool. Ferroptosis, therefore, results in failure of GPX4 function, e.g., by direct inhibition (RSL3, FIN56, and other lethal compounds) or by depletion of the cellular GSH pool. GSH requires cystine to be imported into the cell through the cystine/glutamate antiporter (referred to as system Xc-minus). Erastin blocks system Xc-minus and therefore induces ferroptosis in sensitive cells. Importantly, in functional cellular units, such as renal tubules, the redox capacity is controlled by NADPH concentrations. NADPH abundance in a dying cell might deplete redox buffers beyond the intracellular compartment of a single cell and deplete a functional syncytium, thereby setting cells next to the one that is dying at risk to ferroptosis. This might explain the phenomenon of synchronized regulated necrosis (SRN).

ses might, at least partially, be mediated by ferroptosis to create an oxygen gradient from the necrotic core of the cancer to the surface cells and thereby drive neovascularization and dedifferentiation of the surface cells. In support of this hypothesis, pancreatic cancers were demonstrated to rely on glutamine supply to provide maximal growth (600) and maintain redox balance (399). However, if high concentrations of intracellular free iron predisposes for cancer cell ferroptosis, this high concentration should equally affect the surface cells, and it remains unclear how this might be prevented by the tumor. Bearing in mind the susceptibility of renal tubules to undergo ferroptosis in a synchronized manner, it is interesting that most ferroptosis-sensitive tumor cell lines derive from the same uretric bud stem cells as renal tubules. All clear cell carcinoma cell lines investigated until today were at least partially susceptible to ferroptosis inducing agents (FINs), such as the GPX4 inhibitor RSL3 (711).

Importantly, recent data highlight a role for ferroptosis in plasticity of the cell state that has been proposed to drive resistance to cancer therapies (658). Obviously, if a cancer is capable of escaping ferroptosis, this exhibits a remarkable survival benefit to the cancer. Ferrostatins might therefore support plasticity of a cancer in long-term applications. In summary, both induction and prevention of ferroptosis are currently discussed as cancer treatment options.

## D. Pyroptosis

Pyroptosis is defined as inflammasome-mediated regulated necrosis that is mediated by gasdermins. Pyroptosis has first and most abundantly been described in macrophages as a necrotic type cell death that is mediated by caspase activity inside inflammasomes (408). Potassium efflux is generally accepted as the common mechanism by which bacterial toxins and particulate matter trigger the NLRP3 inflammasome (464). In addition, potassium efflux is also promoted by activation of caspase-11 to indirectly activate the NLRP3 inflammasome (553). It is beyond the scope of this review to list the stimuli of inflammasomes in general, and the reader is referred to excellent recent reviews on this topic (304, 316, 332, 409, 412, 518). Inflammasome activation in the context of necroinflammation has best been described for caspase-1/-11-dependent maturation of the proinflammatory cytokines IL-1$\beta$ and IL-18 from pro-IL-1$\beta$ and pro-IL-18, respectively (124a, 664). Pyroptosis is thought to be mediated by plasma membrane pore formation mediated by the active, cleaved $NH_2$-terminal fragment of gasdermin D (GSDMD) (3, 128, 392, 565). In cell culture time lapse videos of GFP-tagged GSDMD overexpressing cells, GFP enrichment of the plasma membrane is observed over several hours until a critical concentration of GSDMD accumulates in the plasma membrane, resulting in extensive subsequent blebbing of the cells which is followed by plasma membrane rupture a couple of minutes later (128), but the precise mechanism of plasma membrane blebbing and rupture are currently unknown. In contrast to these experiments, in liposomes, GSDMD clearly forms pores that have been identified by several groups by means of electron microscopy (3, 128, 392). Currently, the hypothesis of pore formation is widely recognized, but we like to point out that the biomedical evidence is limited to liposomes and has not been conclusively demonstrated in cells. Therefore, alternative explanations should not be entirely neglegted. Biochemically, it is known that the cleaved $NH_2$-terminal fragment of GSDMD binds to $PIP_2$ in the plasma membrane (295, 583). Importantly, the two major functions of the inflammasomes, cytokine maturation and gasdermin D cleavage, appear to happen in a mechanistically distinct fashion, as oligomerized ASC (an inflammasome component) is required for IL-1$\beta$ maturation whereas oligomerization-deficient ASC may allow gasdermin D-cleavage (125). **FIGURE 4** provides an attempt to summarize the current knowledge of how pyroptosis signaling may be examplified. Gasdermin-dependent regulation of necrosis is currently under extensive investigation by several groups (236, 295, 410, 583, 655, 663), and it will be interesting to follow this work in the future to unravel the most burning open questions in this field: What is the role of the many remaining members of the gasdermin family? Does gasdermin D deficiency in mice reveal the role of pyroptosis in disease models of autoimmunity, sepsis, ischemic injury, and others? Will specific inhibition of inflammatory caspases provide a novel therapeutic strategy for these diseases? What other inflammatory cytokines besides IL-1$\beta$ and IL-18 are matured and secreted during pyroptosis, and is there a release mechanism other than plasma membrane rupture?

## E. Interconnection Between Necroptosis, Ferroptosis, and Pyroptosis

Several nodes of interconnection between RN-pathways have been suggested, but until today, none of these appears to merge into a single common downstream mechanism of regulated necrosis. Beyond the models in which gasdermin D and pMLKL may or may not directly form pores in the plasma membrane, unifying models that are currently discussed include the *1*) master regulation of caspase-8, *2*) redox metabolome, and *3*) $PIP_2$-mediated loss of plasma membrane integrity. These "alternative explanations" to execution of regulated necrosis are discussed because pore formation by either pMLKL and gasdermin D has never been demonstrated in cells; the evidence is entirely limited to highly artificial liposome investigations.

### *1. Model of caspase-8 as the master regulator of necroinflammation*

In apoptosis, the role of caspase-8 homodimers is very clear. When caspase-8 is stabilized (239, 265), the homodimer efficiently cleaves effector caspases to mediate apoptosis. However, if caspase-8 is absent or targeted by either viral or synthetic molecules, necroptotic signaling (see above) can occur because of the loss of function of a caspase-8/cFLIP-long heterodimer. This heterodimer might represent a master regulator of cell death and inflammation **(FIGURE 5)**. In addition, it is increasingly clear that caspase-8 is an upstream regulator of pyroptosis, at least of inflammasome signaling (12, 39, 218, 221, 265). Therefore, caspase-8 might represent a master regulator of inflammation. Limitations to this model include the absence of a role for caspase-8 in ferroptosis, as far as we know today, and the differences in the murine and the human system with respect to mice, that unlike humans, lost caspase-10 during development. It has hardly been investigated in detail which roles in RN-regulation in human cells are taken over by caspase-10 or caspase-10/caspase-8 heterodimers.

### *2. Model of the redox metabolome as a common downstream feature of regulated necrosis*

We proposed a model referred to as the redox metabolome in 2014 (646a). According to that model, changes in the buffering capacity of cells that undergo programmed cell death including both apoptosis and regulated necrosis lose their capacity to efficiently prevent peroxidation. However, recent data suggest that at least in the case of

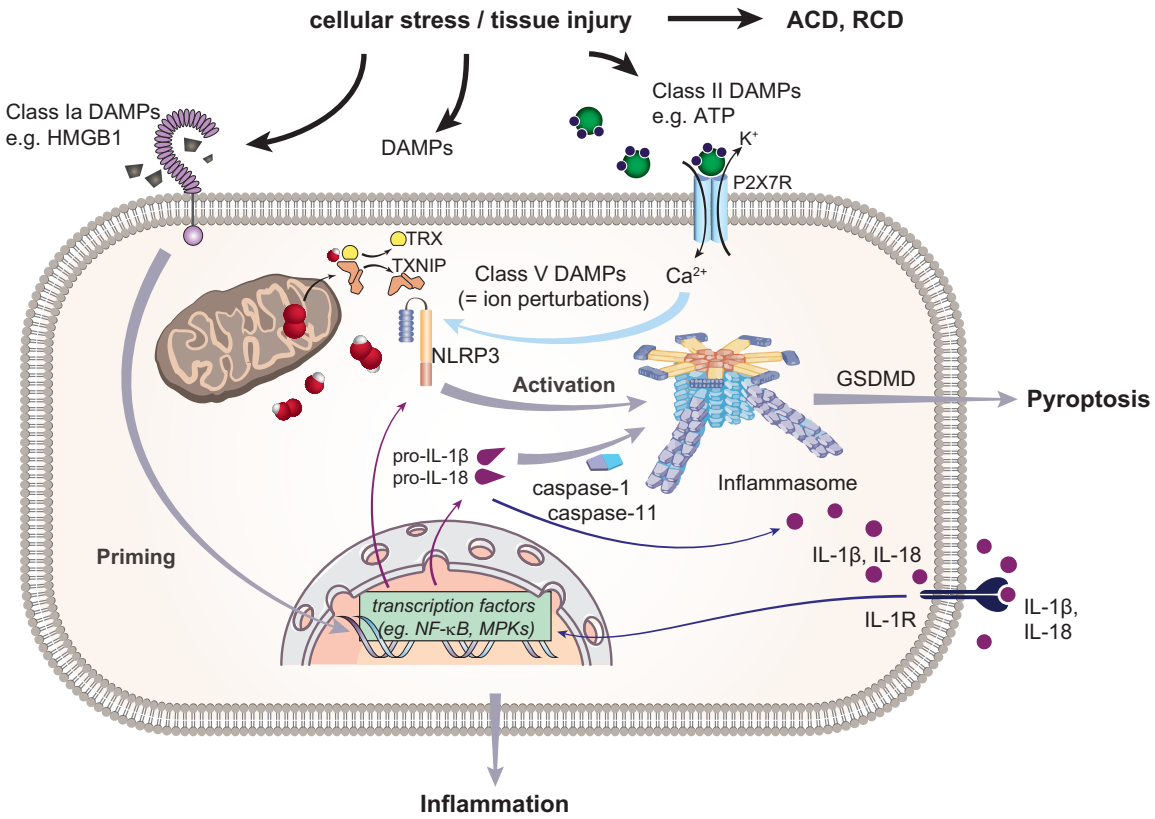



**FIGURE 4.** Pyroptosis signaling. Inflammasome engagement results in the functional recruitment of caspase-1 that is capable of cleaving pro-IL-1$\beta$ and pro-IL-18 to increase the intracellular concentration of IL-1$\beta$ and IL-18. The release of these long-lasting proinflammatory cytokines, however, might require plasma membrane rupture. Caspase-11 homodimers are capable of cleaving gasdermin D (GSDMD). Cleaved GSDMD binds to $PIP_2$ (and other lipids) in the plasma membrane, and its plasma membrane concentration increases the longer the inflammasome is active. Within a couple of hours, in cell lines, GSDMD concentrations at the plasma membrane reach a critical threshold that results in a process of blebbing and plasma membrane rupture, resulting in the release of DAMPs, IL-1$\beta$, and IL-18. It is beyond the scope of this review to list the triggers of inflammasome signaling, but some of the NLRP3-activating mechanisms have been indicated. Pyroptosis, as a means to defend against bacteria, might result in systemic inflammation and possibly represents the most immunogenic cell death described so far. It should be pointed out that Pro-IL-18 signaling is constitutively expressed and that certainly, there are other pathways of transcription-independent inflammasomes activation. Indeed, alternative explanations favor caspase-11 and caspase-1 to function in distinct inflammasomes referred to as noncanonical and canonical, respectively. In such a model, however, these pathways are functionally linked by the cleavage of GSDMD by caspase-11, the insertion of GSDMD-Nterm in membrane, drop in cytosolic calcium/potassium sensed by NLRP3, and activation of caspase-1.

ferroptosis, loss of NADPH abundance is downstream of lipid peroxidation in ferroptosis (218, 265, 588, 633). Limitations to this model are the potential nonspecificity and loss of redox capacity as an artificial epiphenomenon that simply occurs after the cell dies. However, it might be of functional and even clinical relevance when organoids and organisms are investigated (218, 265, 588, 633).

### *3. Model of $PIP_2$-mediated loss of plasma membrane integrity*

A unifying model for necroptosis, ferroptosis, and pyroptosis has not been proposed until today. However, given pMLKL oligomerization at the plasma membrane and its binding to $PIP_2$ during the late stages of necroptosis, functionally $PIP_2$ becomes depleted from the rest of the plasma membrane to a certain extent. Modification in the concentration of $PIP_2$ in the membrane may affect the tethering function of $PIP_2$ to the cytoskeleton (218, 265, 538), resulting in uncoupling of pieces of the membrane from the cytoskeleton and potentially blebbing. Interestingly, bubbles that form from the plasma membrane have been observed during necroptosis (Green and Linkermann, unpublished observation). It is therefore possible that $PIP_2$ depletion might represent a mechanism to regulate the terminal steps of necroptosis before membrane blebbing and rupture, possibly through an attempt of membrane repair.

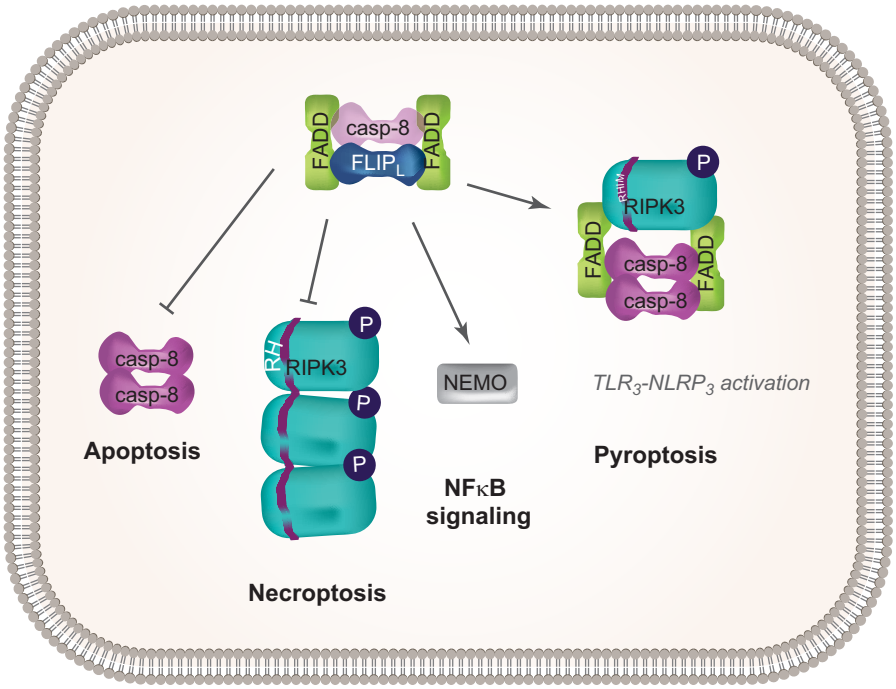



**FIGURE 5.** Control of regulated necrosis by the caspase-8/FLIPlong heterodimer. The caspase-8/FLIPlong heterodimer clearly represents the favored stoichiometric assembly compared with a caspase-8 homodimer. It therefore counteracts apoptosis signaling and FLIPlong expression, e.g., downstream of NF-κB signaling, has been described as a survival signal. However, the heterodimer also counteracts necroptosis by interfering with the assembly of the necrosome. It appears that the heterodimer also regulates NF-κB signaling directly and might control pyroptosis signaling. Therefore, this heterodimer represents a master regulator of cell death and inflammation, and targeting this function by compounds or viral proteins might result in cellular damage.

Likewise, it is predominantly $PIP_2$ that is targeted in the plasma membrane during pyroptosis by the $NH_2$-terminal fragment of gasdermin D, as nicely shown by time lapse imaging. Importantly, an ~5-min period of extensive blebbing precedes the plasma membrane rupture in these videos. Finally, besides phosphatidylethanolamine, $PIP_2$ is a major target in ferroptosis as it is among the most peroxidized lipids during this process. Peroxidation may result in the loss of tethering capacity to the cytoskeleton, and indeed, in the very first time lapse videos that have been published, blebbing-like features have been observed before plasma membrane rupture. **FIGURE 6** briefly introduces this concept. However, as attractive as this model may be, it remains entirely unclear how blebbing might sensitize cells for necrotic plasma membrane rupture. In addition, concentration-dependent inactivation of $PIP_2$ that functionally results in blebbing needs to be shown in much more detail.

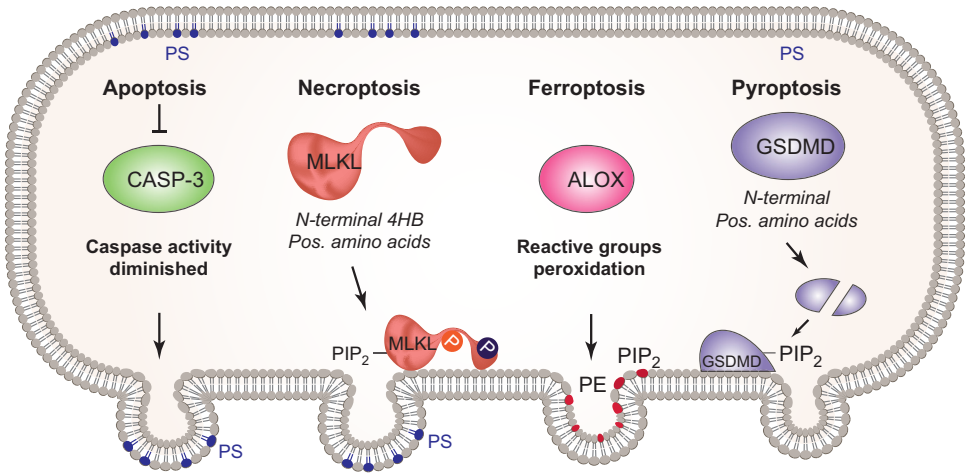



**FIGURE 6.** Membrane blebbing in pathways of regulated cell death. Based on evidence from time-lapse videos, no pathway of regulated necrosis does not include membrane blebbing at certain stages of cell death progression. Whereas described in detail for apoptosis, we are only beginning to understand membrane blebs in necroptosis (formation of annexin V-positive exosomes, potentially reflecting a process of membrane repair), ferroptosis (anecdotal observations of blebs hours before plasma membrane rupture), and pyroptosis (extensive cellular blebbing minutes before plasma membrane ruputure following accumulation of gasdermin D fragments at the plasma membrane). Understanding of the membrane protrusion mechanisms in all of these pathways and the role of phosphatidylserine (PS), phosphatidylethanolamine (PE), and $PIP_2$ in this process may be key to detect common downstream signals in RCD pathways.

## III. A CLASSIFICATION OF DAMPs

### A. The World of DAMPs

As pointed out in the introduction, **TABLE 1** provides a novel classification of DAMPs. The data that led to this suggested model of DAMPs were based on many studies that investigated the mode of DAMP recognition and the cell death modality involved in this process. We consider these two facts the most important processes in the concept of necroinflammation (13, 20, 26, 29, 43, 52, 57, 59, 70, 88, 100, 103, 105, 132, 151, 152, 163, 169, 172, 183, 186, 190, 195, 197, 204, 205, 209, 210, 234, 237, 247, 250, 252, 254, 257, 262, 269–271, 283, 288, 293, 309, 318, 325, 333, 334, 342, 343, 350, 353, 355, 361, 372, 394, 400, 406, 418, 426, 447, 452, 454, 458, 474, 491, 503, 506, 510, 521, 527, 532, 539, 547, 566–568, 571, 577, 579, 585, 604, 611, 617, 627, 629, 630, 638–640, 646, 651, 684, 129, 698, 694, 676, 682, 691, 693, 699, 704, 712, 713, 731–733, 734, 739, 753). We are fully aware of other attemps of DAMP classification that are justifiable and sensible in their respect, but significantly different from our approach (50, 75, 179, 192). Nevertheless, the nomenclature of necroinflammation remains confusing. For example, DAMPs that activate PRR-expressing cells are rarely differentiated from DAMPs that amplify the response, e.g., by members of the IL-1 cytokine family and type I IFNs (421).

### B. Class Ia DAMPs

These are the best described, prototypic DAMPs, including HMGB1 (343, 617, 639), heat shock proteins (HSPs) (20, 342, 452), S100A8/A9 proteins (521, 571), nucleic acids (269, 685, 734), or proteoglycans (568). Class Ia DAMPs are sensed by PRRs on several cell types, and very prominently on cells of the innate immune system. Pattern recognition receptors that are capable of sensing this class of DAMPs include TLRs as the default receptors. In addition, C-type lectin receptors (CLRs) and nucleotide-binding oligomerization domain (NOD) as well as leucine-rich repeat receptors (NLRs) and retinoic acid-inducible gene 1 (RIG-I)-like receptors (RLRs) are members of this broad system.

Absent in melanoma 2 (AIM2)-like receptors and cGMP-AMP (cGAMP) synthase (cGAS) alongside with the receptor for advanced glycation end products (RAGE) complete the arsenal of receptors that sense class Ia DAMPs (139, 223, 269, 294, 360, 514a, 599, 643, 693, 741). Class Ia DAMPs signal danger to the surrounding PRRs-bearing cells such as phagocytes to trigger sterile inflammation, and to PRR-bearing DCs to elicit adaptive immunity. In addition, these DAMPs activate sessile PRR-bearing cells, mostly members of the innate immune system, but also including fibroblasts, myofibroblasts, epithelial, and vascular cells. This exemplifies how repair and regeneration are promoted by DAMPs and how a wound-healing process following infectious/sterile injury-induced inflammation may be initiated (10, 66, 473, 515, 641, 736).

Of note, besides promoting inflammatory processes via various innate immune mechanisms, class Ia DAMPs considerably contribute to the creation of an inflammatory milieu as soon as they trigger NLR members that are upstream regulators of inflammasomes (151, 129, 316, 645, 409, 226, 266, 71, 561, 743, 308, 61, 260, 411). Inflammasomes are higher-order structures inside the cytoplasm that orchestrate both cell death in the form of pyroptosis and inflammation. Inflammasome formation requires apoptosis-associated speck-like protein containing a CARD (ASC) as an adaptor protein, to allow caspase oligomerization which is required for proteolytic cleavage of pro-IL-1$\beta$ and pro-IL-18 to their mature bioactive forms (151, 316, 409, 645, 129). As discussed above, pyroptosis involves inflammasome formation as well (316, 409). Caspase-8, caspase-1, caspase-11, and receptor-interacting protein (RIP) kinases are associated with inflammasome function. Whereas caspase-8 may function as a negative regulator of RIPK3-mediated NLRP3 activation (285), caspase-1 and caspase-11 are centrally involved in inflammasome function and are required for downstream effects (see above).

Accumulating evidence suggests that ubiquitination and phosphorylation control the degradation and thereby the activation status and dynamics of inflammasomes (409). Inflammsomes such as pyrin domain containing 3 (NLRP3) and AIM2 have been characterized as DAMP sensors (61, 71, 151, 226, 260, 266, 308, 409, 411, 561, 129, 743). Two major steps in the activation appear to be of importance. The first signal, known as "priming," is accomplished by receptors including TLRs, which, for example after recognition of class Ia DAMPs such as HMGB1, activate transcription factor NF-$\kappa$B. Nuclear translocation of NF-$\kappa$B is involved in the subsequent expression of NLRP3 and the cytokine pro-IL-1$\beta$ and pro IL-18, but also in the production of the pro-survival protein FLIP-long.

A special case of DAMPs are histones (250, 293) that are released whenever a cell undergoes necrosis, and in the particular case of release of neutrophil extracellular traps (NETs). Histones significantly contribute to pathophysiology of thrombosis, liver disease (251), and renal disease. In the kidney, histones and NETs exacerbate acute kidney injury (327, 476) as they are sensed by either TLR2 and TLR4 (7) or can activated the NLRP3 inflammasome (6). Similarly, histones appear to contribute to the pathophysiology of necrotizing ANCA vasculitis (268) and may be important for renal transplants as they were demonstrated in transplant perfusates (649). In addition, histones have been detected in patients with ARDS where they may be therapeutically targeted (695).

### C. Class Ib DAMPs

Another class of DAMPs, denoted here as class Ib DAMPs, also promotes phagocyte-mediated inflammation and DC-translated adaptive immunity by binding to other sets of recognition molecules, defined here, quite arbitrarily, as "nonclassical" innate immune receptors. These sensing molecules include but are not limited to scavenger receptors (SRs) and purinergic receptors.

Scavenger receptors consist of diverse panoply of integral membrane proteins and soluble secreted extracellular domain isoforms that are structurally diverse and participate in a wide range of biological functions. These innate immune receptors are expressed predominantly by myeloid cells and recognize a variety of ligands (516, 726). An important scavenger receptor is the molecule CD91 that has recently gained special attention as an important receptor on DCs to facilitate engulfment of antigens thereby contributing to the development of adaptive immunity, and in particular, antitumor immunity (69, 375). A crucial class Ib DAMP recognized by CD91 is calreticulin (CALR), an ER-based chaperone that when outside of the ER has emerged to exert an explosion of crucial functions from the cell surface and extracellular environment (211, 532).

Endogenous purines may stimulate P1 and P2 receptors. Pyrimidines are best known for regulatory effects on contraction of smooth muscle cells and vesicle movement regulation. These may affect neurological, immunological, and platelet aggregation function alongside with cardiac function (533). P2 receptors are expressed throughout several tissues and were found to be implicated in innate or adaptive immune responses. P2 receptors have been studied in further detail and classified as ionotropic P2X receptors (P2XRs) that are nucleotide-gated ion channels and G protein-coupled metabotropic P2Y receptors (P2YRs; Refs. 129, 254, 487, 667). Some P2XRs are associated with cell death, whereas this is not the case for P2YRs (254).

The endogenous ligands for purine receptors acting as DAMPs, ATP, ADP, UTP, UDP, and adenosine, can be released from different cell types (64, 534). In fact, the current attentiveness of these "purinoceptors" in the field of innate immunity is due to the observation that stressed or severely damaged cells actively secrete nucleotides, particularly eATP and monosodiumurate (MSU) that predominantly function as signaling molecules by purinergic P2 receptor activation (206, 525).

P2X purinoceptors are nonselective membrane ion channels preferably permeable to sodium, potassium, and calcium that open upon binding a ligand within milliseconds (487). P2X7 receptors have been the most intensively investigated because their activation by eATP is a key step in the release of IL-1$\beta$via secondary activation of the NLRP3 inflammasome as described in the following.

P2YRs belong to the GPCR family. They consist of an intracellular COOH terminus and an extracellular $NH_2$ terminus as classical seven transmembrane receptors. At least eight mammalian P2YRs were cloned (P2Y1/2/4/6/11/12/13/14R) with more likely awaiting discovery (1). The DAMP eATP functions as a ligand for these receptors. Macrophages and monocytes respond to "find-me" signals that include ATP-mediated P2Y2R signaling (152, 254). Finally, P2Y2R signaling may contribute to general leukocyte functions including cytokine production and migration (for detailed reviews, see Refs. 152, 254).

### D. Class II DAMPs

A class of molecules that activate the canonical NLRP3 inflammasome will be referred to as class II DAMPs. They include eATP, $K^+$ ionophores (419), MSU, pyrophosphate and cholesterol crystals, or factors that cause lysosomal destabilization (242, 422). These activators are sensed without NLRP3 ligation, but still are capable of triggering inflammasome formation, IL-1$\beta$ /IL-18 release, and pyroptosis (151, 266, 409, 440). Indirect activation of the NLRP3 inflammasome by class II DAMPs in cooperation with class I DAMPs has been discovered in various disorders, including metabolic syndrome, type 2 diabetes, atherosclerosis, gout, reperfusion injury of the heart, neurodegeneration such as Alzheimer's disease, chronic kidney diseases, and macular degeneration (718). A pivotal role in NLRP3 inflammasome assembly has to be ascribed to eATP that shows a unique feature among all members of the DAMP family and may be regarded as a "hybrid DAMP." In fact, eATP indirectly leads to canonical NLRP3 activation under involvement of P2X7 and hemichannels of pannexin-1 (151, 266, 129, 713). eATP may initially engage P2X7 to change cellular iron composition, in particular $Ca^{2+}$ influx and $K^+$ efflux. See below for class V DAMPs as homeostatic DAMPs (179). In fact, $K^+$ efflux has been intensively investigated as a trigger of NLRP3 inflammasome activation. In addition to eATP, all of the other NLRP3 activators may decrease cytosolic $K^+$ levels (464), however without a clear mechanistic insight (519). NLRP3 inflammasome engaged by eATP does not represent a uniformly activated principle among immune cells. In DCs, TLR stimulation does not require eATP to mature IL-1$\beta$ and IL-18 (71, 129, 151, 266, 409, 713). In addition, oxidative stress, most likely from mitochondria, and ER stress participate in the activation of NLRP3 inflammasomes. For example, ROS-mediated oxidative stress, derived from mitochondria or induced by ER stress, has been shown to serve as important inflammasome coactivating signals (151, 179, 226, 266, 561, 718). The thioredoxin-interacting protein (TXNIP) system exhibits another example of an adaptor molecule for NLRP3 (161, 151, 226, 266, 308, 561, 743). In addition, gasdermin D (GSDMD), a capsase substrate, is required for induction of pyroptosis and IL-1$\beta$ and IL-18 release (236). As far as we understand, there is no sorting motif for IL-1$\beta$

and IL-18 to be directly secreted in the presence of a functional plasma membrane. Altogether, however, while these molecular mechanisms (and some more not described here) have been proposed for activating NLRP3, a unified model has yet to gain acceptance.

Unlike the NLRP3 inflammasome, the AIM2 inflammasome directly senses dsDNA. Therefore, the AIM2 inflammasome does not need a second signal in terms of class II DAMPs. AIM2 is capable of recognizing self (endogenous) DNA in addition to microbial DNA (260, 411). For example, alterations of the nuclear envelope integrity are reportedly found to cause the exposure of endogenous nuclear DNA in the cytosol to promote the activation of the AIM2 inflammasome. Nuclear envelope stress can therefore directly engage innate immune sensors to elicit inflammation (127a).

## E. Class III DAMPs

Natural-killer group 2, member D (NKG2D) defines class III DAMP recognition. Induced DAMPs in this class are presented and sensed by the very same cells that are stressed, and auto-activated as immune effectors. Predominantly, natural killer cells express NKG2D, but the expression is not strictly limited to these effectors. Indeed, $\gamma\delta$ T cells and $CD8^+$ T cells may be included to sense class III DAMPs, and also certain $CD4^+$ lymphocytes have been assigned comparable functions (27, 28, 70, 353, 529). Class III DAMPs recognition by such receptors is characterized as polymorphic. Therefore, sensing of class III DAMPs is based on mechanisms that are comparable to HLA sensing, albeit less complex by a number of magnitudes (70).

## F. Class IV DAMPs

Class IV DAMPs are classically represented by neo-epitopes that may be found upon oxidative injury. Such oxidation-specific epitopes (OSEs) encompass a common set of epitopes present on various oxidatively modified self-proteins and self-lipids. These DAMPs are exposed on cells following ischemia-reperfusion injury in affected tissue as well as on necrotic/necroptotic cells, microvesicles, and damaged structures such as oxidized low-density lipoproteins (oxLDLs) lipids. As so far detected, OSEs include non-muscle myosin heavy chain II (NMHC-II), actin cytoskeleton, oxidized phospholipids (oxPLs), and malondialdehyde (MDA)-modified amino groups (52, 79, 447, 584, 638, 732, 733).

In stressful pathological situations, in which reactive oxygen species (ROS) are produced in excess, OSEs accumulate and bind to PRRs to promote sterile inflammation, a typical example being postischemic reperfusion injury. In fact, OSEs ligate a panel of cellular recognition receptors most of which are expressed by macrophages including TLRs and scavenger receptors but also soluble innate humoral recognition receptors such as pentraxins and proteins of the complement system (52, 387, 682).

Of special importance is recognition of OSEs by another class of humoral innate PRRs, namely preexisting natural IgM (nIgM) antibodies. Thus nIgM antibodies in human umbilical cord blood, which represent naive natural antibodies of fetal origin, have been shown to possess specificity for OSEs (97). Of note, as shown in studies of intestinal and heart ischemia-reperfusion models, OSEs such as NMHC-II activate autoreactive natural IgM antibodies to induce the MBL-mediated cascade of the complement system (153, 362, 584, 733).

## G. Class V DAMPs

Homeostatic danger signals form the family of class V DAMPs (179). They reflect subtle changes in the microenvironment during the steady state of a cell. These changes include hypoxia-induced redox imbalance and intracellular acidosis, as seen in cells that are sensitive for ferroptosis. Therefore, it is not surprising that ER stress has been linked to these conditions. An overview of this concept is provided in **FIGURE 7**. Class V DAMPs induced by intracellular ion perturbations such as intracellular $K^+$ efflux (464) or hyponatremia-associated low osmolality (307) are sensed to induce inflammasome signaling. When combined with significant ER stress, the protein kinase R (PKR)-like ER kinase (PERK) becomes a dominant player in this signaling cascade to instigate an UPR (660, 661). However, the exact molecular mechanisms of these sensing processes are still elusive.

## H. Class VI DAMPs

Recent insights into intracellular metabolism in DCs and macrophages have provided new notions about a contributing role of metabolism-derived DAMPs in the activation of these key cells of the innate immune system. This class of metabolic DAMPs is denoted here as class VI DAMPs. Intriguingly, both cell types have been shown to be sensitive to metabolic reprogramming. Hypoxia and alterations of the nutrient state (and therefore autophagy) and a response to DAMP-triggered activation of PRRs exhibit classical examples. In fact, the activation process of DCs and macrophages is metabolically characterized by a switch towards glycolysis and away from oxidative phosphorylation (OXPHOS), similar to the Warburg effect ("aerobic glycolysis") in tumors (297, 488). One of the key features of metabolic reprogramming in macrophages is the accumulation of the tricarboxylic acid (TCA) cycle intermediate succinate that operates as an intracellular metabolic DAMP. Succinate stabilizes the transcription factor hypoxia-inducible factor

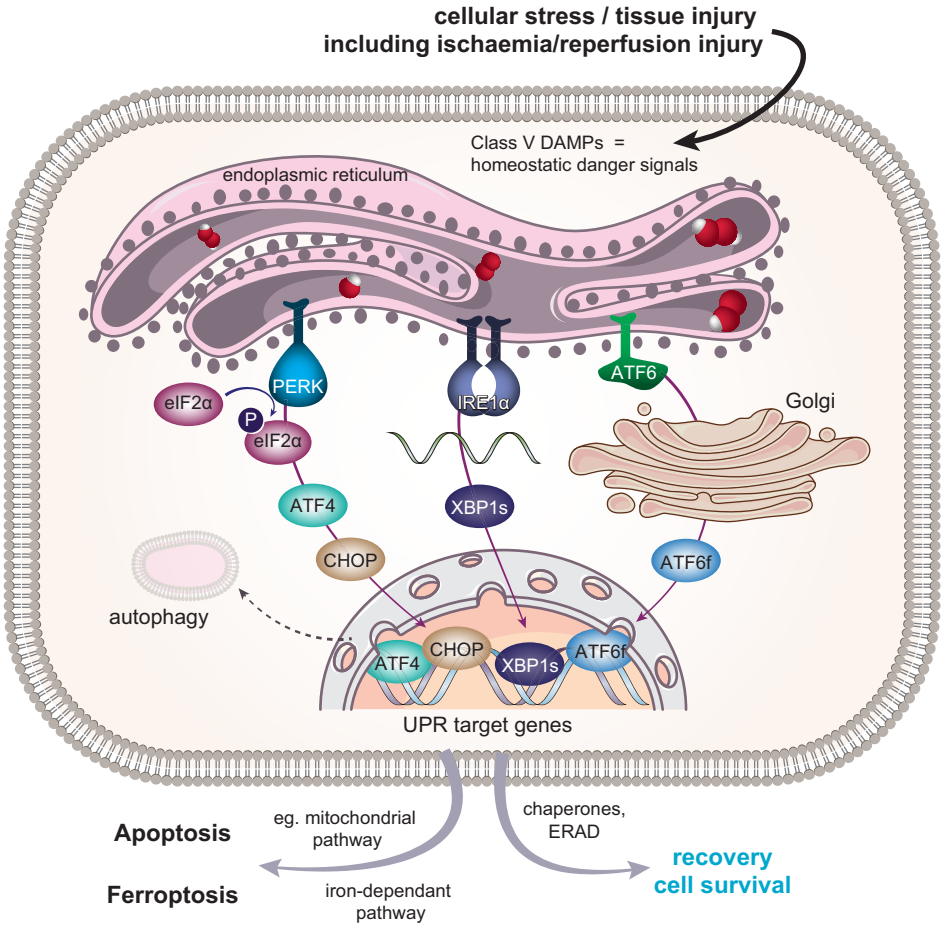



**FIGURE 7.** ER stress and DAMPs. DAMPs that refer to homeostatic danger signals, defining an altered pattern of molecules in terms of dyshomeostasis-associated molecular patterns, are depicted in this figure. Diverse extracellular conditions and changes in intracellular homeostasis may result in ER stress. This complex condition appears to be of outmost clinical relevance because ER stress may be among the earliest events that may be recognized following the changes of intracellular pH.

1α (HIF-1α), thereby promoting the switch to glycolysis and driving inflammation via secretion of IL-1β and under involvement of the NLRP3 inflammasome (for details of this inflammasome, see above). Mechanistically, HIF-1α appears then to induce IL-1β directly because the gene promoter for IL-1β contains a HIF-1α-binding site (109, 297, 488, 618). Of note, succinate has also been shown to operate as an extracellular DAMP when recognized by the "nonclassical" PRR G protein-coupled receptor 91 (GPR91) (17, 117a, 208, 552).

## I. Class VII DAMPs

Another class of DAMPs, denoted here as class VII DAMPs, is involved in the process of nociception that can be regarded as a new branch of the innate immune defense system. In fact, pain acts as a protective mechanism to prevent injury to tissues and prompts an individual to react to remove or escape the painful stimulus (65, 703). Nociception is the process of transmission of painful signals by nociceptors (that is, specialized primary sensory neurons essential for the perception of pain) in the primary afferent nerve fibers, which specifically respond to noxious stimuli. These noxious stimuli are detected by nociceptors and converted into electrical signals, which are then transmitted to the spinal cord, thalamus, and cerebral cortex, via the discriminative pain pathway, leading to the final perception of pain (141, 170). In fact, several of the TLRs and RAGE have been implicated to play key roles in pain signaling (289). However, there appear to exist special "nonclassical" PRRs including GPCRs (202, 500) and transient receptor potential (TRP) ion channels (112).

Notably, TRP ion channels have emerged as a family of evolutionarily conserved ligand-gated ion channels that function as molecular detectors of various external stimuli, including mechanical perturbation and changes in temperature. Several members of this family, at least six channels from three TRP family subtypes [transient receptor potential vanilloid subtype 1–4 (TRPV1–4), transient receptor potential cation channel subfamily M member 8 (TRPM8), and transient receptor potential cation channel subfamily A member 1 (TRPA1)], are expressed in nociceptors, where they act as transducers for danger signals from thermal, chemical, and mechanical stimuli and play crucial roles in the generation and development of pathological pain perception (112, 445, 504).

There is growing interest in this new branch of DAMP research, and one of the best studied receptors out of the

TRP family able to transmit pain via sensing of cellular stress and tissue injury refers to TRPA1 (reviewed in Ref. 654). TRPA1 is a nonselective cation channel expressed in mammalian peripheral pain receptors of neuronal and non-neuronal tissues, and a unique aspect of its function is a remarkable ligand promiscuity towards danger signals when operating as a polymodal detector of both endogenous and exogenous/environmental class VII DAMPs. For example, osmotic challenges, low and high temperature, and in the case of the *Caenorhabditis elegans* homolog of TRPA1 even light, as well as a host of natural and industrial chemical irritants and mechanical forces are known to activate TRPA1 channels (reviewed in Refs. 485, 654, 755).

Another important receptor loaded on nociceptors is TRPV1, which responds not only to exogenous class VII DAMPs substances such as capsaicin, the pungent ingredient of the hot chilli pepper (175), but also to endogenous class VII DAMPs, for example, certain oxidative lipid metabolites including oxidative linoleic acid metabolites (OLAMs) as well as oxidative arachidonic acid metabolites (OAAMs) (505, 593). This kind of modern DAMP research in nociception impressively shows that the peripheral nervous system is obviously integrated in the innate immune system, and there is an emerging notion that class VII DAMP-triggered TRP channels in cooperation with the other classes of DAMP-triggered PRRs play an important role in maintain and restore homeostasis.

## IV. DAMP-INDUCED INNATE ALLOIMMUNITY

### A. The Unavoidable Injuries to an Allograft in the Donor and the Recipient

"Injury induced allograft rejection": since this original proposal (338), increasing attention has been given by transplant clinicians to the various forms of damage to allografts depending on a given donation procedure such as donation after brain death (DBD), donation after circulatory death (DCD), the use of extended criteria donors (ECD), and living related/unrelated donors. In all those procedures, allografts are potentially exposed to various injuries starting from the gradually varying shape of the organ donor and ending up with the uniform act of implantation-associated postischemic reperfusion in the recipient. In DBD donors, the strength of multiple injuries to an allograft depends on conditions in the organ donor, that is, *1*) the kind and degree of the cerebral accident, *2*) the duration and organ-damaging episodes of the subsequent critical care period before and under brain death condition, and *3*) the time period of organ preservation and the maneuver of final implantation-associated postischemic reperfusion in the recipient. Of note, during the critical care period (under continuous mechanical ventilation) on the intensive care ward, the ("still vital") innate immune system of this category of donors has plenty of time to get activated to induce an acute systemic autoinflammatory syndrome associated with the maturation and activation of fully activated mature intragraft DCs which consequently are transplanted within the inflamed organ to the recipient (for details, see below).

DCD donors suffer from prolonged warm ischemia times during cardiac arrest associated with (time-dependent) anoxic/hypoxic damage to the donor organ that is aggravated during postischemic reperfusion in the recipient. Of note, while the organs are more ischemically damaged, the innate immune system of this category of donors is not turned on to get activated, that is, there is no systemic inflammation and no activation of donor-derived DCs. This circumstance may explain the observation that renal allografts removed from DCD donors, despite an increased incidence of delayed graft function (DGF) of 73% compared with 27% in DBD donor kidneys (469), show a similar rate of acute rejection episodes as well as no differences in long-term outcome when compared with kidneys from DBD donors (358b, 606, 662). Likewise, liver and lung allografts removed from DCD donors have also been demonstrated to show results comparable to those with standard brain dead donors (136, 324). DCD donors, as also extended criteria donors, have been suggested to be more vulnerable to IRI since donor kidneys suffer from prolonged warm ischemia time, increased donor age, or comorbidity of the donor (554).

As generally known, allografts from living donors do much better than from DBD and DCD donors, generally appreciated to be due to shorter cold ischemia times (484). In fact, despite HLA disparity, the rejection and survival rates of living unrelated renal transplants under modern immunosuppressive protocols are comparable to those of living related kidney allografts (94). Certainly, these transplants are by far less damaged compared with DBD and DCD, and not inflamed and without activated DCs compared with DBD.

In any case, during postischemic allograft reperfusion in the recipient, two different innate immune systems, that of the donor and that of the recipient, are activated, mounting an intragraft sterile inflammatory response and leading to an adaptive alloimmune response in the recipient. The key event of this scenario refers to the activation of donor-derived DCs already residing in the allograft (i.e., in DBD) as well as recipient-derived DCs entering the donor organ during reperfusion in the recipient. The aim in this section is to analyze the various DAMPs that modulate donor- and recipient-derived DC functions and explore how those DAMPs may contribute to pathways leading to an adaptive alloimmune response. Since ischemia/reperfusion-induced injury associated with the emission of DAMPs is inescapable in solid organ transplantation and involves activation

of DCs, studies on nontransplant IRI models will also be included in this review.

In summary, the first injury to an allograft occurs already in the organ donor. Here, we will highlight the development of ROS-mediated oxidative stress under brain death conditions because it is defined as an innate immunity-promoting injury as demonstrated in both experimental models and DBD donors. The default injury to an allograft may include changes as ROS-mediated IRI in the recipient, highlighting the importance of ferroptosis in this setting. Undoubtedly, oxidative injury during postischemic reperfusion is a complex scenario that includes but is not limited to disturbed energy metabolism, cellular changes of the mitochondria and cellular membranes, instigation of stress responses and, as mentioned above, various forms of cell death, that is, cellular pathologies which serve as critical sources of DAMP emission.

### *1. Oxidative stress drives inflammation in brain dead donors*

A decade ago, early studies in rat suggested an influence the dead or dying brain (BD) condition on allograft dysfunction (517). In these experiments, long-term survival of brain-dead donor isografts and allograft was shown to be significantly less compared with living donor grafts. In addition, the transcription of cytokines was found to be markedly increased in all brain-dead donor grafts. More recently published evidence demonstrates donor BD to be inevitably associated with loss of redox potential, including ER-stress and ferroptosis-like cell death to be critical mediators of innate immune system activation. Ultimately, by triggering necroinflammation, such conditions might result in an acute SIRS (68, 148, 319, 358, 417, 457, 575, 602). Necroinflammation, in a setting like this, may be associated with the detection of a certain signature of necrotically dying cells in the graft (68, 53, 370, 417, 508, 576, 603). In particular, HMGB1 and HSP70 have been associated with such conditions (15, 322, 555), but PRRs and their corresponding machinery (90, 322, 550) as well as fragments of the complement system (115) are likely to contribute. Finally, proinflammatory cytokines such as IL-1$\beta$ and IL-18 (328, 358, 614) may indicate ongoing pyroptosis, and CxCR1 (116)and IL-33 may represent a necroptotic response. Cross-priming to mature DCs may consequently follow during transplantation (450, 650). Interestingly, in those studies on human splenic DCs, three conventional DC subsets and one plasmacytoid DC subset were identified (450).

### *2. Ischemia-reperfusion injury and the redox system*

As mentioned at the beginning, the critical influence of ischemic injury on acute and chronic allograft rejection events has been investigated for decades and was analyzed in an early clinical trial for renal transplant recipients (338, 349, 350). In recent years, these findings have been confirmed by others (499, 558, 613, 666, 677, 692). While a variety of molecular mechanisms have been proposed to explain the phenomenon of IRI, excess production of ROS continues to receive most attention as a critical factor in the genesis of this kind of oxidative injury. In fact, since the time of publication of the first clinical trial, production of ROS during IRI has been confirmed in IRI models and human renal allografts (167, 343, 350). In this scenario, ferroptosis is the most likely reason for ROS production in IRI. It has been widely accepted that vascular cells are at the edge of hypoxic injury and $H_2O_2$ and superoxide anion generation. Within minutes after reperfusion, and upon reoxygenation of the tissue, vascular ROS (vROS) may set the stage for the disease to progress (280, 343, 344, 350, 612).

Infiltrating monocytes and macrophages, as well as neutrophils (nROS) that may be seen in the graft within minutes following reperfusion, are thought to add further oxidation events to the stressed tissue (78, 259, 280), ultimately resulting in necroinflammation. In addition, nROS may reactivate vascular cells which, in turn, produce vROS again, a phenomenon originally described by researchers as the "vicious circle" of IRI (433). ROS production is certainly not limited to these two mechanisms, as the involvement of changes in the electron transport chain (ETC), xanthine oxidase (XO), nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXes), and several others contribute to the microenvironmental challenge (11, 34–36, 76, 96,138, 216, 228, 343, 344, 456, 530, 545, 549, 562, 642, 754). In conclusion, the seconds/minutes during removal of organs from living or deceased donors as well as the early phase of reperfusion by blood of the recipient reflect a transient hypoxic state. Studies on a model of hypoxic reperfusion of the ischemic heart support this concept by showing significantly higher ROS production in the more hypoxic tissue, in contrast to lower ROS production upon higher myocardial tissue oxygen tension (11). This concept is summarized in **FIGURE 8**. This concept also takes into consideration the many recent reviews on ROS in IRI (216, 280, 343, 384, 549, 592, 686). The role of the DNA damage response in this scenario may represent a consequence of the loss of redox buffers (110, 111, 178, 298, 390, 404, 574, 591, 705, 717), and the loss of NADPH abundance may decrease the threshold for several pathways of regulated necrosis, including necroptosis and ferroptosis, in this setting (280, 384, 385, 738). As cellular demise is regulated by ER stress (106, 184, 248, 306, 329, 389, 634, 674, 738) in a balancing act with autophagy (8, 77, 280, 363, 369, 379, 425, 430, 523, 623, 631, 686), the complexity of the regulation of necrosis during transplantation becomes obvious. However, it will be required to unreveal this system in a much more complete manner to therapeutically optimize the inevitable sensitization to acute allograft rejection and antibody-mediated rejection (see below).

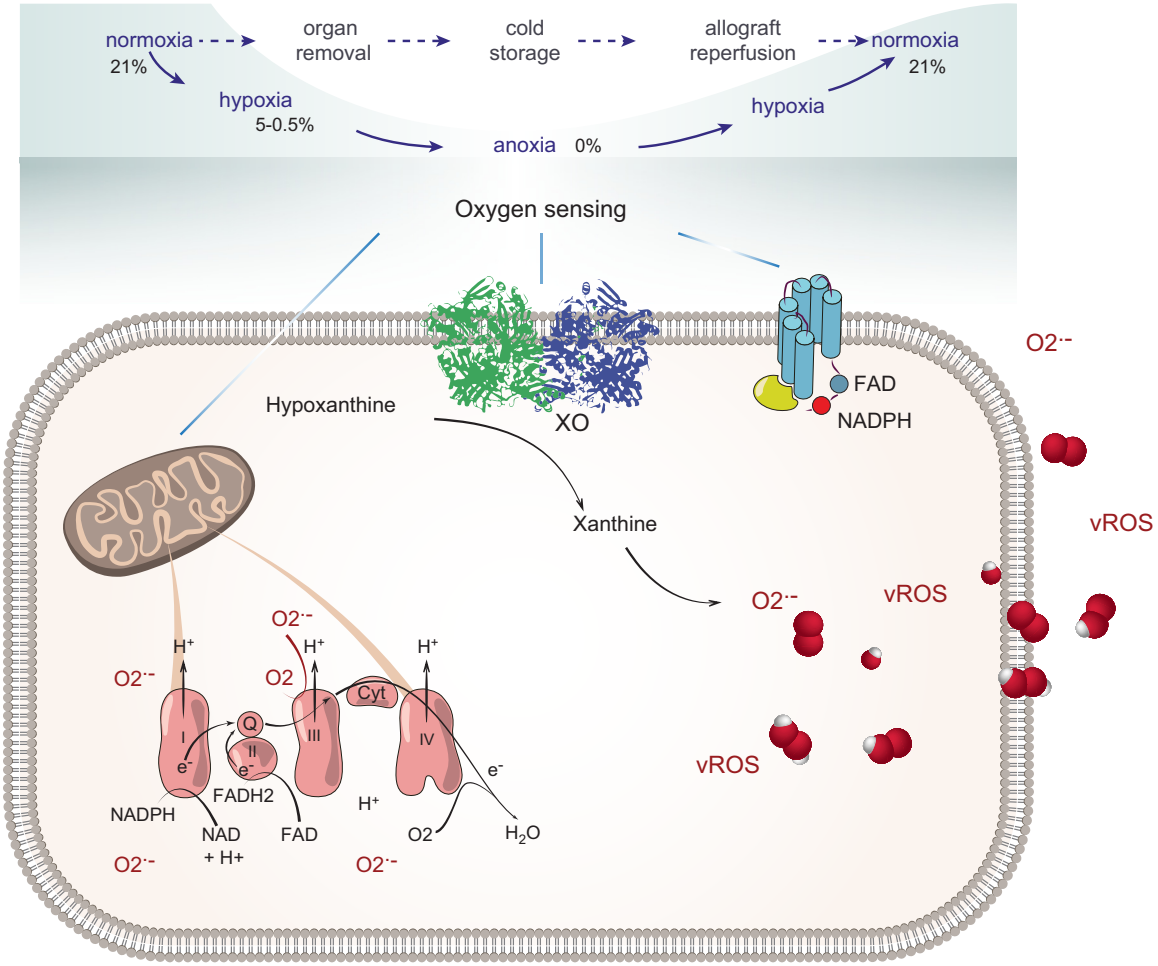



**FIGURE 8.** Oxygen sensing and ROS production during solid organ transplantation. ROS production in postischemic tissues involves enzymes that are capable of reducing molecular oxygen to form superoxide ($O2^{-}$) and/or hydrogen peroxide. This results in the subsequent release of ROS. Three hypoxia-sensing systems, the mitochondrial electron transport chain (ETC)-associated enzymes (mainly through complex I and III), xanthine oxidase (XO), and the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXes) have been ascribed predominant pathophysiological relevance. This system may be of outstanding importance for solid organ transplantation, but similar mechanisms have also been detected in solid tumors.

## B. Oxidative Injury Induced Cross-Priming and Its Contribution to Necroinflammation

Antigen engulfment and processing by steady-state immature DCs (iDCs) and their subsequent DAMP-promoted, PRR-triggered maturation into immunostimulatory DCs able to prime naive $CD4^+$ T cells represents the key event of oxidative injury-activated innate immunity as a trigger of adaptive immunity. Innate alloimmunity mediating allograft rejection is a unique immunological variant in that priming of recipient alloreactive T cells with alloantigens is provided by donor-derived and recipient-derived immunostimulatory DCs via the direct, indirect, and semi-direct pathway (direct, indirect, semi-direct allorecognition) (240, 343, 350, 598, 692).

The fundamental process of stress/injury-induced, DAMP/PRR-mediated DC maturation in peripheral tissues is characterized by a striking metamorphosis of these master antigen-presenting cells. The large-scale changes include the upregulation of the major histocompatibility complex (MHC) and costimulatory proteins, initiating signal 1 and signal 2, respectively. In addition, the secretion of Th1-polarizing cytokines (signal 3) promotes naive $CD4^+$ T cells to differentiate into IFN-γ-secreting Th1 and secretion of Th17-polarizing cytokines into IL-17-secreting Th17 cells. Furthermore, migratory factors, such as C-C chemokine receptor type 7 (CCR7), force DCs to migrate to the host's distal secondary lymphoid organs to present processed peptidic antigens to naive T cells. Instruction by mature DCs about antigens involved and the type of peripheral cell stress and/or tissue injury enables naive T cells then to mount a specific "tailor-made" adaptive immune responses (113, 343, 556, 665).

A crucial role of DAMPs in the generation of immunostimulatory DCs under various conditions of sterile inflammation

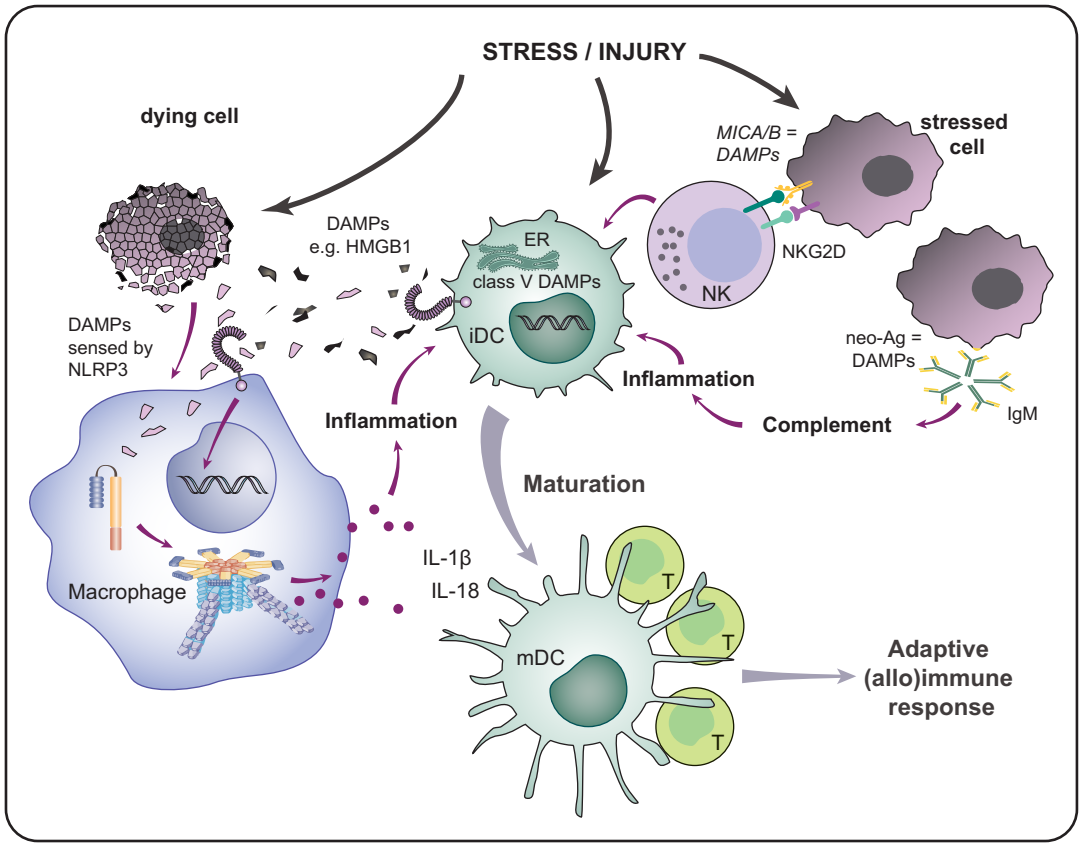



**FIGURE 9.** DAMPs and DC maturation. Simplified model depicting the role of DAMPs (class Ib DAMPs not considered) in the maturation/activation of immunostimulatory DCs to migrate to secondary lymphoid tissue and induce an adaptive T-cell (allo)immune response. DAMPs, damage-associated molecular patterns; DC, dendritic cell; ER, endoplasmic reticulum; iDC, immature dendritic cell; IgM, immunoglobulin M; IL-1$\beta$, interleukin-1$\beta$; mDC, mature DC; MO, macrophage; neoAg, neo-antigens; NK cell, natural killer cell; NKG2D, natural killer group 2 member D; NLRP3, NOD-like receptor family, pyrin domain containing 3; T, T cell; TLRs, Toll-like receptors.

including IRI has been reported (468). The role of DCs in necroinflammation is depicted in **FIGURES 9 AND 10**. These scenarios will be outlines for each DAMP class in the following. Compare **TABLE 1** for an overview of the seven classes DAMPs as defined in this article.

### *1. Class Ia/Ib DAMPs*

Following recognition of class Ia DAMPs, PRRs on/in iDCs such as TLRs trigger signaling pathways that directly promote the acquisition of their immunostimulatory properties (16). Oxidative stress, for example, associated with IRI promotes the emission of this class of DAMPs, a process that can be regarded as the key event in converting iDCs to mature DCs **(FIGURE 10)**.

A key class Ia DAMP is nuclear HMGB1 that regulates chromatin structure and gene transcription, while cytosolic HMGB1 is involved in inflammasome activation and autophagy. HMGB1 can be either actively secreted or exposed by cells undergoing a life-threatening stress or released from necrotic cells (343, 617, 639, 651). Once released in the extracellular space, the protein can bind to PRRs such as RAGE, TLR2, TLR4, and TLR9, thereby mediating and promoting tissue inflammation. Convincing evidence has shown that HMGB1 is generated in organs upon IRI including human kidney allografts (435, 468, 605, 617, 624, 639, 720), but also emitted upon brain death (282, 322, 555, 702). In fact, it appears that oxidative stress is a central regulator of HMGB1's translocation, release, and activity in sterile inflammation and cell death including necrosis, apoptosis, autophagic cell death, and pyroptosis (720).

On the other hand, HMGB1 promotes DC maturation, thereby promoting Th1 cell polarization (145, 146, 366, 416, 436, 707, 750). According to the data from these studies, HMGB1, mainly via recognition by its cognate receptor RAGE, can be regarded as a strong immunostimulatory DAMP for DC-mediated cross priming, necroinflammation, and subsequent T cell-mediated adaptive immunity. Importantly, however, it is understood that HMGB1 by itself, upon injection of the recombinant protein, is not sufficient to initiate necroinflammation (Linkermann et al., unpublished observation).

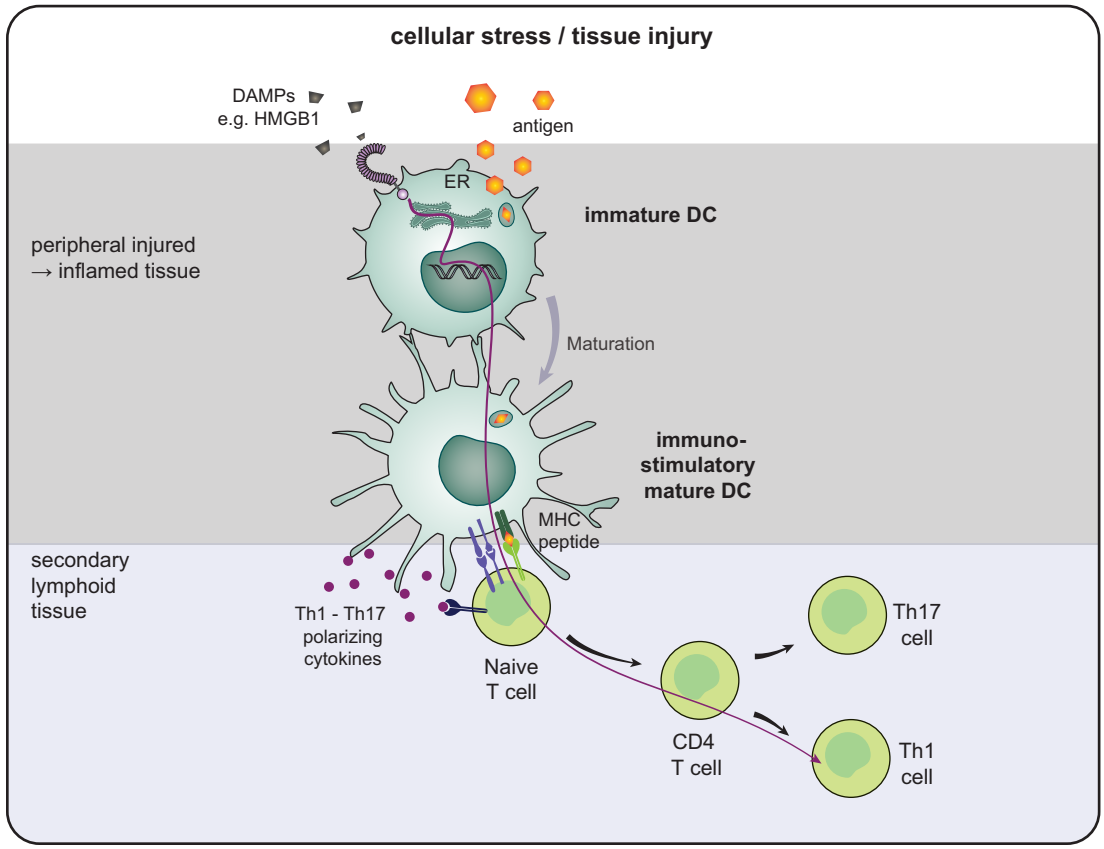



**FIGURE 10.** Class Ia DAMPs triggering a Th1-immune response. Simplified and exemplified scenario model of how a class Ia DAMP (here HMGB1) triggers an intra- and intercellular pathway (red dotted line) resulting in promotion of a Th1 immune response via activation of immunostimulatory dendritic cells. DAMPs, damage-associated molecular patterns; DC, dendritic cell; HMGB1, high mobility group box 1; MHC, major histocompatibility complex; Th, T helper cell; TLR, Toll-like receptor; TCR, T-cell receptor; UCM, upregulated costimulatory molecules.

In addition to HMGB1, HSPs play a critical role as class Ia DAMPs in the initiation of sterile inflammatory processes including IRI-mediated inflammation. Thus numerous studies on animal models but also in transplant patients have shown upregulation of HSP expression, in particular, HSP70, following ischemia and/or IRI but also under brain death condition (15, 51, 161, 220, 342, 343, 350, 489, 512, 646b, 735). Similar to HMGB1 and as shown in other lines of studies, HSP70 family members, via binding to TLR2 and TLR4, promote maturation of immunostimulatory DCs able to elicit Th1 responses (21, 47, 157, 158, 272, 616). In addition, promoting TLR4-triggered DC maturation, HSPs also contribute to mounting an adaptive immune response by facilitating direct and cross-presentation of antigens released from dying cells by DCs (748).

Class Ia DAMPs also refer to "self" nucleic acids present in the cytosol where they are sensed by binding to PRRs including TLR3, TLR9, NLRs, RLRs, and ALRs (234, 514a, 537, 599, 643). Nucleic acids may be released during IRI via IRI-associated processes of apoptosis and necroptosis (280, 384). Of importance with regards to mechanisms of ICD-induced adaptive antitumor immunity (see below), the DAMP dsRNA, recognized by TLR3 to trigger Toll IL-1 receptor (TIR) domain-containing (TRIF) signaling, has been shown to be released during IRI (87).

Furthermore, nucleic acid-sensing receptors such as TLR3 and TLR9 have been shown to promote DC maturation (249, 415) providing supportive evidence to the notion that IRI-associated release of nucleic acids may also contribute to DC maturation.

In addition, components of the damaged extracellular matrix shown to be released during injuries including IRI (350) can be included in the category of class Ia DAMPs. These molecules include fragments of hyaluronan, heparan sulfate, and HS proteoglycan and were also demonstrated to promote TLR4-triggered DC maturation (267, 463, 620).

It remains unclear whether the class Ib DAMP CALR emitted during IRI-induced ER stress, oxidative stress, or as a consequence of hypoxia/reoxygenation and exposed on the cell surface contributes to DC maturation in these experimental settings (184, 248, 306, 329, 389, 532, 609, 634, 670, 701, 737, 738). On the other hand, in another line of

experiments in mice, a recombinant CALR fragment has been shown to operate as a potent stimulatory agent to DC maturation in a TLR4/CD14 and PI3K/Akt-dependent pathway (372). Further experiments are needed to clarify this topic.

### 2. Class II DAMPs

The close connection between innate immunity-induced inflammatory and subsequent adaptive immune responses led to the debate whether or not activation of the inflammasome complex, including class II DAMP-induced activation of the NLRP3 inflammasome, provides instruction by immunostimulatory DCs to the adaptive immune system in a similar manner to other PRRs. To date, there is only indirect and limited evidence in support of this notion (99, 388). Class II DAMPs appear to contribute to DC maturation in a more indirect way by creating an inflammatory milieu required for DCs to gain full immunostimulatory properties. This may be partially mediated by the NLRP3 inflammasome and pyroptosis as a potent producer of IL-1$\beta$ (388, 556). Accordingly, class II DAMPs, in particular eATP but also MSU, alum, and cholesterol, are known as non-pathogen-derived second signals for NLRP3 inflammasome activation promoting the creation of sterile tissue inflammation (4, 30, 73, 151, 154, 212, 217, 226, 257, 308, 409, 542, 544, 645). Moreover, several studies indicate ATP release from dying cells upon ischemic injury (254, 255). Along these lines, ATP appears to be implicated in activation of the NLRP3 inflammasome (212, 257, 393, 560, 632, 668). Interestingly, a recent study on the hypoxia/reoxygenation model found that eATP was able to induce maturation of human monocyte-derived DCs (74).

A cautious synopsis of these findings gives rise to the assumption that class II DAMPs such as eATP, via creation of inflammasome-dependent inflammation, may contribute to DC maturation. Nevertheless, studies on IRI models to demonstrate a direct role of class II DAMPs in maturation of DCs are still tenuous.

Interestingly, apart from studies on IRI models, earlier experiments on the effects of alum on DCs in adaptive immunity provided the first evidence suggesting that this DAMP via induction of the DAMP uric acid contributes to DC maturation, a finding at least pointing to a role of the NLRP3 inflammasome in DC maturation (317, 585).

In view of the fact that eATP indirectly activates the NLRP3 inflammasome via promotion of ion perturbations ($K^+$ efflux), recent studies are interestingly showing that ion efflux and influenza infection trigger NLRP3 inflammasome signaling in human DCs (166).

Finally, there is a recently reported study on graft versus host disease (GvHD) in mice demonstrating that condition therapy-induced class II DAMPs (uric acid) activate, as second signals, the NLRP3 inflammasome, which subsequently promotes IL-1$\beta$-dependent activation of (donor) DCs to elicit an allogeneic Th17 response leading to GvHD (261).

### 3. Class III DAMPs

Class III DAMPs such as MICs and ULBPs (28, 70, 353, 459) on stressed cells activate NKG2D-expressing NK cells. NK cells are important regulators of DC function during the course of immune responses. In addition, NK cells shape adaptive immune responses. They promote DC maturation and influence the T-cell responses (164, 165). Mouse IRI studies as well as murine in vitro cell culture models of hypoxia/reoxygenation indicate a central role for oxidative stress in the regulation of various NKG2D-binding class III DAMPs (57, 88, 163, 237, 343, 398, 678). This hypothesis may be underlined by data that have described NK cells as an infiltrate of human transplants. Interestingly, this occurs as soon as the organ is removed from brain-dead donors (478, 572). In addition, one clinical analysis of human kidney biopsies suggested the expression of MICB before and after transplantation (526). Those results suggested that NK cells may become activated via stress-inducible DAMPs under brain death conditions. In addition, in studies on tumor models, DNA damage response (DDR) was shown to promote upregulation of class III DAMPs (200, 331, 358a, 539, 601). Similarities between antitumor immunity and alloimmunity obviously exist. Consequently, DDR is involved in cellular responses to oxidative stress and IRI (404, 705).

### 4. Class IV DAMPs

Class IV DAMPs can directly or indirectly contribute to DC maturation via initial binding to natural IgM antibodies. This process is followed by activation of the complement cascade (52, 153, 584, 732, 733). In the scenario of experimentally induced IRI, induction of complement activation appears to use each of the three major pathways [classical, mannose binding lectin (MBL), and alternative pathway] depending on the experimental IRI model investigated, the MBL pathway obviously playing a prevalent role, and the alternative pathway mostly amplifying the cascade (23, 159, 343, 434, 581).

Once complement is triggered, the so-called membrane attack complex (MAC, C5b-9) may result in regulated necrosis of the target cell (745). However, it is a matter of debate if the MAC results in the formation of a pore in the plasma membrane. Necrosis induced by complement may in fact depend on internalization of the MAC (J. Pober, personal communication). However, the plasma membrane rupture is thought to release DAMPs of the classes I–III and thereby promote necroinflammation (507, 721, 744). In addition, complement cleavage products, such as C3a and C5a, may

function as chemoattractants or may stimulate DCs directly (368). Complement-mediated lysis, therefore, exhibits a classical example of regulated necrosis that drives necroinflammation.

#### 5. Class V DAMPs

As compared with class IV DAMPs, also class V DAMPs stimulate DCs. ER stress and changes in redox homeostasis may trigger DCs in addition to the DAMPs. If ER stress occurs in the DCs themselves, it may accelerate DC maturation given the involvement of the UPR sensors (397, 496, 740, 749). Other class V DAMPs may lead to functional expression of other classes of DAMPs. Such a process may upregulate the class Ia DAMP HSP70 by DCs in response to heat. This may subsequently result in the upregulation of costimulatory molecules, proinflammatory cytokines, and T cell-mediated immune responses (314). There is also compelling evidence that oxidative stress-associated IRI leads to ER stress, thereby emitting class V DAMPs to initiate the UPR (77, 106, 184, 248, 306, 329, 373, 389, 389, 448, 634, 674, 609, 738).

#### 6. Class VI and class VII DAMPs

As mentioned above, succinate has also been shown to operate as an extracellular DAMP when recognized by GPR91 (17, 117a, 208, 552). For example, DCs sense extracellular succinate through this receptor and the increase in intracellular $Ca^{2+}$ downstream of this event synergizes with TLR3 or TLR7 signaling to promote DC activation and their migratory ability (488, 552). These studies are conceptually important because they illustrate that DCs have evolved to integrate DAMPs emitted from stressed, damaged, or dying cells with metabolic DAMPs to regulate immunogenicity, a scenario that, along with others, also points to the mitochondria and NLRP3 machinery being closely interwoven at multiple levels (718). Briefly, we believe that DAMPs that are sensed by nociceptors should be mentioned as a class VII. The classification of DAMPs is summarized in **TABLE 1**. The authors of this review like to point out that a classification of DAMPs may reflect a useful tool for the mechanistic understanding and that other useful ways to classify DAMPs may be discussed.

## V. DAMP-INDUCED PATHWAYS MEDIATING AN ANTI-TUMOR IMMUNE RESPONSE

### A. A Peculiar Type of Cell Death Induces Anti-tumor Immunity

The concept of cancer immunosurveillance by the immune system has been proposed more than five decades ago (63, 625). In brief, immunosurveillance proposes that precancerous or cancerous cells when arising are sensed as "altered (mutated) self" by antigen-presenting cells which instigate an immune response to eliminate these malignant cells. Originally based on poor evidence, the concept continued to gain increasing credibility given genetic and functional methodological improvements. Today, an increasing amount of data have been published in support of the cancer immunosurveillance hypothesis. One such prominent evidence refers to a particular kind of an injury to cancer cells denoted as "immunogenic cell death" (ICD) in terms of a certain functionally peculiar type of RCD that is induced by certain antineoplastic therapies. Of note, ICD is associated with the generation and emission of DAMPs that have been shown to induce specific antitumor immunity. In fact, there is now convincing preclinical and accumulating clinical evidence in support of the notion that successful use of antineoplastic agents involves the immune system (321, 752). In addition, recent data on the role of DAMP-activated NKG2D-bearing NK cells in antitumor immunity have added another level of direct support to the immunosurveillance concept. We will address this scenario in more details in the following sections.

### B. Role of DAMPs in Immunogenic Cell Death

#### 1. Immunogenic cell death

Grounded on the danger/injury model, a conceptual revolution in oncology has occurred in that tumors are considered to be entities that can be detected and efficiently eliminated by the immune system under certain circumstances. The quintessence of this new concept specifically refers to the phenomenon of ICD (192). However, only a few lethal stimuli may directly trigger ICD including certain chemotherapeutics (e.g., anthracyclines), oxaliplatin, UVC radiation and radiotherapy, certain oncolytic viruses [e.g., Newcastle disease virus (NDV)], high hydrostatic pressure, photodynamic therapy (PDT) (e.g., hypericin-PDT), and RIG-I-like helicases ligand (192). These are called "ICD inducers" (188). Their precise mode of action is not quite clear, but there is accumulating evidence indicating that these therapeutic inducers cause ICD, at any rate, through ER stress associated with or induced by ROS (193).

In the current era in which cancer immunotherapy has grown to be the most promising new cancer treatment approach since the development of the first chemotherapies in the late 1940s, the use of ICD inducers offers a significant additional therapeutic quality, especially in combination with immune checkpoint therapy (203, 446). This concept has already been endorsed in an experimental setting using clinically relevant genetic mouse models. In this study, a combination of selected clinically approved immunogenic chemotherapeutics triggering $CD8^+$ T-cell infiltration into tumors was shown to make unresponsive tumors sensitive

to checkpoint blockade therapy. Interestingly, this drug-induced antitumor T-cell response was associated with an upregulation of TLR4 on a distinct subset of tumor-infiltrating DCs, presumably activated by HMGB1 released from dying tumor cells in this model (509). Certainly, these data are promising and open the door to new perspectives in expanding the proportion of patients being responsive to current anticancer immunotherapy, yet concerns about overactivated autoimmunity under such a treatment are expected.

As typically demonstrated in targeted experiments, ICD is associated with emission of a series of DAMPs that develop in a precise spatiotemporally defined configuration. This coordinated emission of DAMPs then triggers a robust antitumor immune response that is associated with the establishment of an immunological memory. The efficient establishment of a specific adaptive response against tumor-associated antigens (TAAs) in the context of ICD relies on the activation of DCs by DAMPs. DCs can encounter tumor cells either through infiltrating tumors (401) or at distant sites when tumor cells that have detached from the tumor mass enter the blood circulation to facilitate their spread to distant locations in the body (689). In fact, studies on the pivotal involvement of DCs employed genetic mouse models and human monocyte-derived DCs (224, 752). Considering the human in vivo situation, recent exploration of the effect of platinum-induced ICD (associated with emission of CALR, ATP, and HMGB1) suggested platinum treatment to drive tumor cell phagocytosis. This appeared to be largely mediated by $CD1c^+$ DCs (124b).

Notably, characteristic for the action of DAMPs in this scenario is that, in addition to promoting immunity, they break, in parallel, the existing tumor-driven environmental immunosuppressive "milieu" reflecting "tumor tolerogenicity." This "suppressive" tumor environment is established in the absence of DAMPs but presence of "tolerogenic" cells including but not limited to $CD4^+$ $CD25^+$ $Foxp3^+$ Tregs and myeloid-derived suppressor cells (MDSCs) (192, 301, 302, 321, 451, 524, 687).

ICD is associated with cellular stress, such as ER stress and lipid peroxidation, that precede the emission of DAMPs to an earlier time point than plasma membrane rupture and necrosis. As recently reviewed (348), these stress responses include ROS↔ER stress-induced UPR (at least in general) and certain innate immune defense processes such as autophagy (189, 192, 196, 301, 302, 321). From the perspective of this article, ROS production and the ER stress as well as UPR-triggered autophagic mechanisms deserve special attention because, as reviewed in Reference 348, they are also involved in models of IRI (77, 106, 118, 184, 248, 280, 306, 329, 343, 369, 379, 389, 430, 609, 623, 631, 634, 674, 686) and, thus, may represent a mechanistic link between allograft and tumor rejection.

### *2. Emission of class Ia/b, class II, and class V DAMPs by cells succumbing to immunogenic cell death*

According to recently published consensus guidelines (302), the phenomenon of ICD is associated with the emission of class Ia/Ib, class II, and class V DAMPs. Thus increasing evidence from studies on models of ICD have shown that the triggering of a pre-mortem ER stress in the dying cancer cell is a crucial capacity of ICD-inducing antineoplastic agents to induce an efficient anti-tumor immune response against TAAs (189, 196, 321). This joint induction of ER stress and loss of redox capacity reflects the emission of class V DAMPs that are perceived by the PERK sensor to elicit, at least in some models, an UPR in the scenario of ICD (241, 548, 573). Experiments with various ICD-inducing antineoplastic agents have shown that ER stress, either accompanied or induced by ROS production in terms of class V DAMPs, are typical features of ICD and seem to be indispensable for subsequent induction of further classes of DAMPs, although their exact molecular cooperation and interaction in efficiently inducing subsequent danger signaling is still elusive (187, 189, 196, 299, 300, 661). Nevertheless, current evidence indicates that ROS overproduction at the ER leads to the highest degree of ER-associated proteotoxicity that translates into the generation of danger signaling pathways in a PERK-dependent manner (187).

Two ER stress-induced key DAMPs, namely, CALR, and eATP, sequentially emitted at different phases of the apoptotic process, have been identified, together with release of HMGB1 and secretion of type I IFN, to be crucial for cancer immunogenicity via activation of tumor-infiltrating DCs (187, 189, 192, 196, 301, 302, 321). **FIGURE 11** exemplifies how these DAMPs are thought to contribute to the concept of necrosinflammation.

A) ER STRESS AND CALR EXPOSURE. In the preapoptotic phase, ICD-inducing therapeutics mobilize ER chaperone CALR to traffic towards the cell surface where it docks on the CD91 on target cells and interacts with the same receptor on DCs. Of note, CALR surface exposure can also be induced in prenecroptotic cells, in the context of NDV-induced ICD (315). The exact translocation pathway to the cell surface has been found to be highly inducer-dependent as demonstrated by a series of studies (192). Trafficking of CALR has been found to be especially mediated by PERK. This includes an interaction with the phosphorylation of eukaryotic initiation factor 2$\alpha$ (eIF2$\alpha$). Chemotherapy-induced CALR exposure pathway tends to be much more complex and multi-factorial compared with Hyp-PDT-induced CALR exposure pathway. The latter is thus far the simplest and most rapid molecular pathway for CALR exposure described in the ICD literature (195). On the other hand, ER stress-induced autophagy in the case of Hyp-PDT induced ICD tends to suppress CALR surface exposure (190). Moreover, there is compelling evidence suggesting a

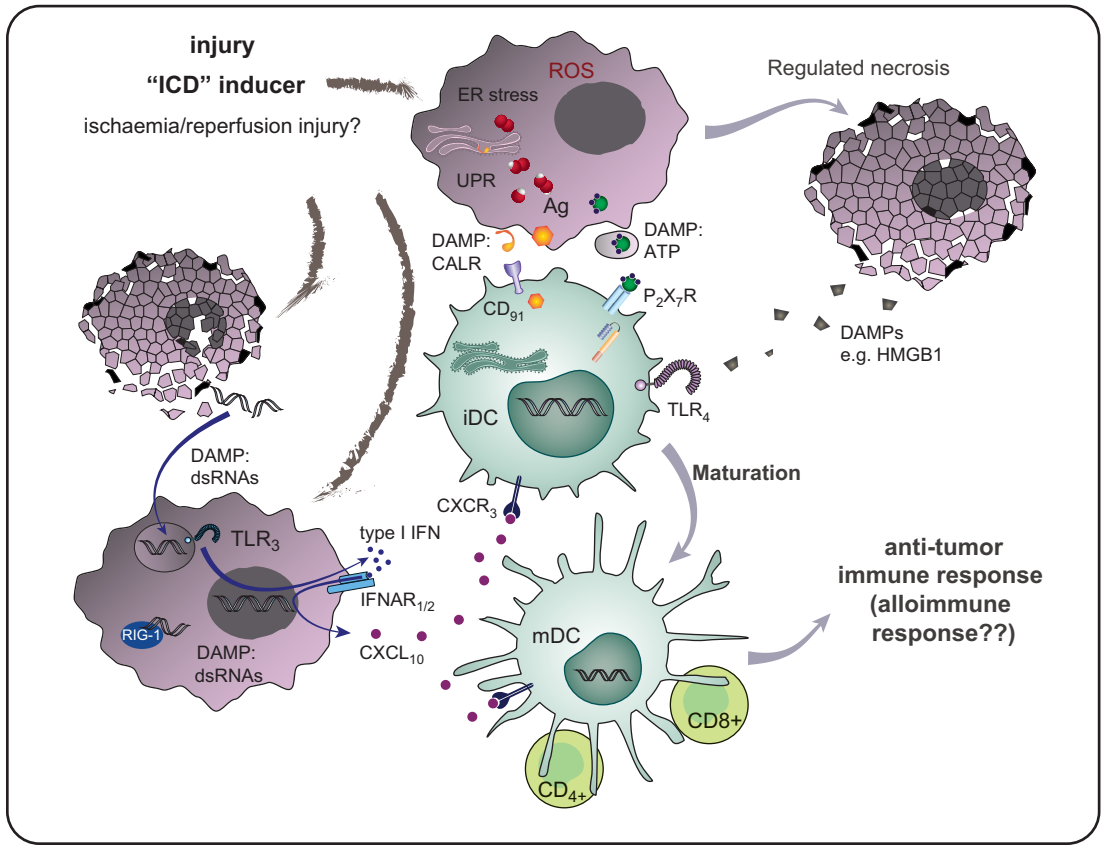



**FIGURE 11.** The concept of DAMP-mediated necroinflammation. Simplified scenario model of therapy-induced immunogenic cell death (ICD) associated with the spatiotemporally defined emission of DAMPs (CALR, ATP, HMGB1) and secretion of type I interferons (type I IFNs). These three DAMPs together with type I IFNs define the immunogenicity of ICD by facilitating tumor antigen uptake by immature dendritic cells (iDC) and promoting upregulation of immunostimulatory capacities of mature dendritic cells (mDC) to activate CD4+ and CD8+ T cells thereby eliciting an anti-tumor immune response. Note: the figure is primarily sketched on the basis of data from studies on immunogenic cell death of cancer cells; the fade-in of the clue to a possible role of ischemia reperfusion injury in such a scenario (leading to an alloimmune response) is purely speculative, though based on data from other lines of studies on models of postischemic reperfusion injury. Ag, (tumor-associated) antigen; CALR, calreticulin; CXCL10, chemokine (C-X-C motif) ligand 10; CXCR3, CXC chemokine receptor 3; DAMP, damage-associated molecular pattern; dsRNA, double-stranded RNA; ER, endoplasmic reticulum; HMGB1, high mobility group box 1; ICD, immunogenic cell death; IDC, immature dendritic cell; mDC, mature dendritic cell; UPR, unfolded protein response; NLRP3, NOD-like receptor family, pyrin domain containing 3; P2X7R, purinergic P2X 7receptor; TLR, Toll-like receptor.

crucial and obligatory role of posttranslational modifications occurring in the course of an UPR. Upon binding to the scavenger receptor CD91, CALR delivers a major phagocytic signal to DCs, thereby improving their capacity to take up dead cell-associated antigens as an important first step to gain full immunostimulatory capacities (32, 142, 189, 195, 207, 300, 326, 501, 502, 661, 683, 688). Moreover, low endogenous CALR levels may translate into low CALR surface exposure that can in turn be responsible for an important resistance mechanism against anticancer immunotherapy (191).

B) SECRETION OF EXTRACELLULAR ATP. During the blebbing phase (for chemotherapy) or preapoptotic phase (for Hyp-PDT) of apoptosis, a class II DAMP, namely, ATP, is secreted to the extracellular space via a yet undefined mechanism (195, 301, 424, 673). ATP secretion, like CALR exposure, tends to be mediated through various signaling pathways in an ICD-inducer-dependent fashion (197). For instance, Hyp-PDT-induced ATP secretion is elicited by a PERK-mediated ER stress pathway culminating into a secretory pathway-based ATP liberation (195). Moreover, this ER-to-extracellular space transport of ATP is not affected by the autophagic machinery (190).

Caspase-mediated opening of pannexin 1 channels may be involved in the secretion of ATP (83, 301, 424, 673). In addition, ATP secretion by cells exposed to chemotherapeutic-ICD inducers was found to require an intact autophagic machinery (25, 187, 363, 374, 423, 443).

ATP, after secretion, promotes the differentiation of freshly recruited immune cells, for example, into tumor-infiltrating DCs. This effect may involve the purinergic receptor P2RY2

(152, 193, 194, 401, 402, 430). Moreover, eATP, primarily acting through P2RX7 during ICD, promotes the activation of the DC-based NLRP3 inflammasome, hence stimulating IL-18 and IL-1$\beta$ processing. Upon release, IL-17-producing $\gamma\delta$ T cells and priming of $CD8^+$ T cells against tumor antigens may occur (24, 30, 32, 73, 83, 129, 154, 189, 204, 207, 212, 326, 374, 401, 402, 423, 443, 444, 542, 673, 683). Of note, in some contexts, P2X7 receptor activation may not have synergistic immunogenic effects but rather more potentiating ones, during ICD (194). Additionally, ATP was found to act also when released by plasma membrane rupture DAMP in the late apoptotic/necrotic phase of tumor cell death (192).

C) RELEASE OF HMGB1. This class Ia DAMP strongly mediates anti-tumor immune responses via chemotherapy-induced ICD. During the post-mortem phase, HMGB1, in a special redox modification and operating as a DAMP, is released upon both the nuclear and plasma membrane permeabilization from tumor cells succumbing to ICD into the extracellular space (13, 627). In addition to mediating inflammation, HMGB1 was published to be involved in the progression of autophagic flux, and as a proposed mechanism, beclin 1 (BECN1) and B cell CLL/lymphoma 2 (BCL2) may be involved (13, 189, 192, 284, 301, 617, 627, 639). This class Ia DAMP, recognized by TLR4, has been shown to assist in effective cross-presentation of tumor-associated antigens, to promote upregulation of their costimulatory molecules, to increase intracellular levels of pro-IL-1$\beta$, and to support the secretion of type I IFNs which, at least in some test models, are also required for ICD (13, 321, 330, 594, 751, 752). HMGB1 was shown to act also as an actively secreted DAMP in the early apoptotic phase, although not in an ICD context per se (192). Interestingly, in a manner similar to HMGB1's activity in cardiac allografting (see above), it was recently reported that also in case of cancer (more specifically glioblastoma), HMGB1-driven anticancer vaccination effect in vivo was strongly associated with increased intratumoral infiltration of Th17 cells apart from Th1 and cytotoxic $CD8^+$ T cells (198).

D) SECRETION OF TYPE I INTERFERONS. Finally, cancer cells release type I interferons (IFNs) upon anthracycline stimulation. In addition to immunostimulatory effects, type I IFNs, via autocrine and/or paracrine signaling, promote secretion of the chemokine CXCL10 which is proposed to recruit DCs to the tumor site (594, 751). TLR3 is activated by its agonist, the DAMP dsRNA (294) probably released during anthracycline-induced ICD. In a similar manner, genotoxic stress in cancer cells has been found to trigger formation of endogenous noncoding RNAs which, via recognition by RIG-I, and innate immune receptorhat facilitates type I IFN responses **(FIGURE 12)** (535).

E) HEAT SHOCK PROTEINS AND DNA. HSP70 and HSP90 instigate a specific cellular anti-tumor response via contribution to maturation of iDCs into immunogenic DCs, thereby promoting presentation and cross-presentation of tumor-associated antigens (TAAs). As plasma membrane receptors on DCs, the scavenger receptor CD91 and TLR4 have been

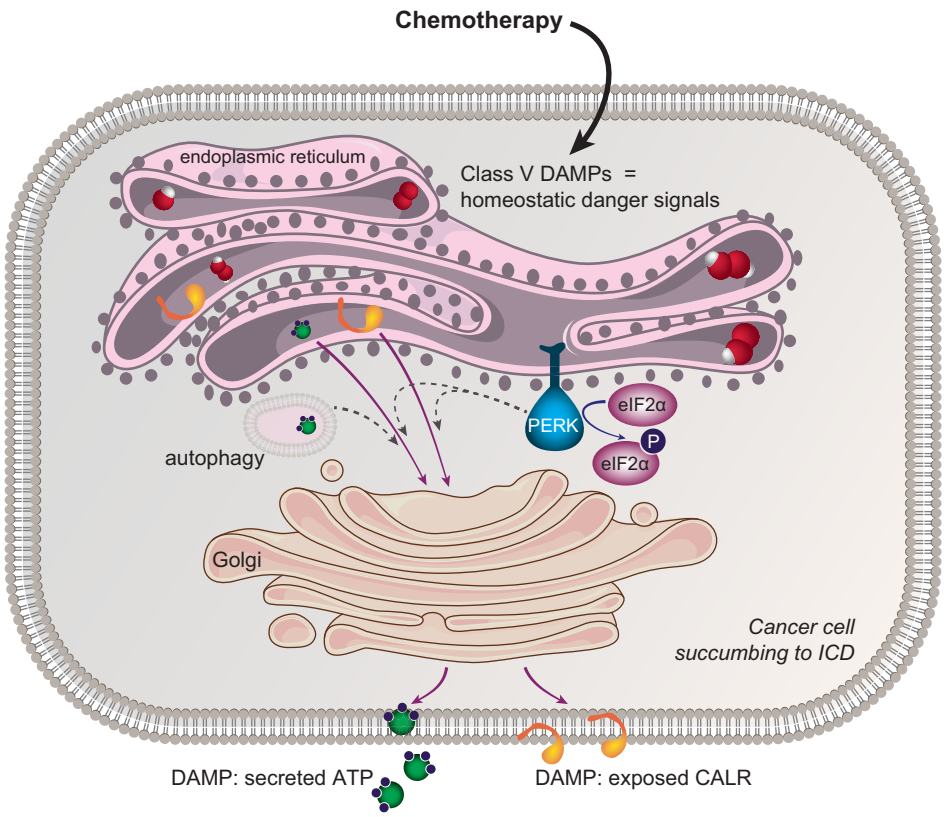



**FIGURE 12.** ICD in a cancer cell. Model of chemotherapy-induced oxidative/ER stress in a cancer cell succumbing to ICD. Class V DAMPs are sensed by the stress sensor PERK that promotes translocation of calreticulin (CALR) to operate as class Ib DAMP at the cell surface and secretion of ATP under involvement of unfolded protein response-mediated autophagic mechanisms to operate as a class II DAMP in the extracellular space. CALR, calreticulin; DAMPs, damage-associated molecular patterns; ICD, immunogenic cell death; PERK, protein kinase-like eukaryotic initiation factor 2$\alpha$ kinase; eIF2$\alpha$, eukaryotic translational initiation factor 2$\alpha$; ROS, reactive oxygen species.

shown to be involved (91,100, 156, 162, 470, 582). For example, HSP70 was shown to be the most important component, followed by CALR and HMGB, in facilitating DC immunity, which suppresses metastases of mouse 4 T1 mammary tumors and prolongs survival of test mice (100, 192, 197, 318, 378, 611, 753). Other lines of recent studies on murine tumor models provided the first evidence suggesting that STING/IRF3 pathway-mediated recognition of DNA of tumor cells by DCs promotes anti-tumor immune responses that are associated with type I IFN secretion and priming of $CD8^+$ T cells (312, 691).

In summary, the current ICD concept in oncoimmunology holds that the spatiotemporally orchestrated emission of DAMPs, when bound to/sensed by their cognate receptors, together with secretion of type I IFNs, promote *1*) the recruitment of DCs to sites of ongoing ICD, 2) their capacity to engulf necrotic debris, *3*) their efficient cross-presentation of TAAs, and *4*) their metamorphosis into immunostimulatory APCs that are able to instigate and maintain an adaptive anti-tumor $CD4^+$/$CD8^+$ T-cell immune response (143, 321, 635, 752).

Current notions in oncoimmunological research further hold that these efferent immune processes proceed in two phases, involving the sequential recruitment and IL-1$\beta$-dependent activation of IL-17-secreting $\gamma\delta$ T cells. This is associated with increased proliferation of $CD4^+$ and cytotoxic $CD8^+$ T cells (403, 427, 752). T-cell immunity results in a number of anti-tumorigenic processes such as antineoplastic effects mediated by secretion of IFN-$\gamma$ and the granzyme-perforin pathway. In addition, these processes lead to the establishment of a protective immunological memory (52, 192, 201, 301, 403, 427, 752).

### C. Class III DAMPs in Immunological Tumor Surveillance

Apart from their role in ICD-induced anti-tumor immunity reflecting a strong principle of potential immune surveillance, DAMPs are reportedly involved in another concept of cancer prevention as a primary function of the immune system. This concept is based on recent knowledge holding that lymphocytes such as NK cells and $\gamma\delta$ T cells are able to recognize and eliminate stressed premalignant cells (418). This process is initiated by the exposure of class III DAMPs on stressed cancer cells such as MICs and UFLBPs. As recently reviewed in more detail (348), class III DAMPs are expressed in many human tumors, including melanoma, leukemia, myeloma, glioma, and carcinomas of the prostate, breast, lung, and colon (418, 539). As mentioned above, these stress-induced molecules are recognized by the germline-encoded activating receptor NKG2D that is expressed by almost all NK cells, $\gamma\delta$ T cells, NKT cells, certain $CD8^+$ T cells, and $CD4^+$ T cells. Remarkably, NK cells, mostly in cooperation with NKT cells and $\gamma\delta$ T cells, have been shown to lyse tumor cells. In fact, accumulating evidence shows that the expression of NKG2D is crucial for tumor cell elimination both in vitro and in tumor transplantation experiments in vivo (353, 418, 459, 539). Moreover, class III DAMP-activated NK cells are potent producers of numerous cytokines. IFN-$\gamma$, in particular, is thought to have powerful anti-tumor activities, such as inducing MHC class I expression and sensitizing tumor cells to $CD8^+$ T cell killing (418). In addition, activated NK cells, via direct cell contact and secretion of cytokines (INF-$\gamma$, TNF-$\alpha$) have been shown in many (though not all) studies to assist in maturation of immunostimulatory DCs in tumors thereby contributing to antitumor immunity (compare **FIGURES 8 AND 9**) (645a, 747).

As also reviewed (348), accumulating evidence suggests that the expression of class III DAMPs is regulated by various stress pathways, in particular, by the DDR, a stress response that plays an important role in the immune surveillance of cancer (98, 258). In fact, the DDR is constitutively activated in many human cancers as a consequence of oncogene-induced "replication stress" (418, 539). Mechanisms involved in this scenario are not well characterized, but it is proposed that damage to DNA leads to the presence of cytosolic DNA that binds to and activates STING-dependent-DNA sensor pathways, which induce the expression of class III DAMPs (200, 229, 358a).

Certainly, with regard to the scenario of ICD-induced antitumor immunity mentioned above, whether or not the pathway of DDR $\rightarrow$ class III DAMPs $\rightarrow$ anti-tumor immunity contributes to the eradication of neoplastic cells responding to chemoradiotherapy in vivo remains to be elucidated. In particular, the issue of whether or not NKG2D–expressing $\gamma\delta$ T cells, known to operate in the context of ICD-induced antitumor immunity, may be activated by ICD-induced class III DAMPs remains elusive.

## VI. A MODEL FOR THE IMMUNOLOGICAL HIERARCHY OF REGULATED CELL DEATH PATHWAYS

The understanding of *1*) the molecular machinery of the signaling pathways of regulated necrosis including specifically released DAMPs and *2*) the specific character of DAMPs allows to predict effects of RCD on the immune system **(FIGURE 13)**. Apoptosis clearly is not associated with systemic inflammation because of several factors that independently escape immune recognition. First, and most importantly, during apoptosis, DAMPs are not released given the maintenance of the plasma membrane integrity. In addition, exposure of phosphatidylserine functions as an eat-me signal for apoptotic cells, a process that does not allow cell death to proceed to secondary necrosis (as seen in vitro after several hours). Apoptosis, therefore, is the ideal pathway to maintain metabolic cellular turnover and cellular turnover that is required during development.

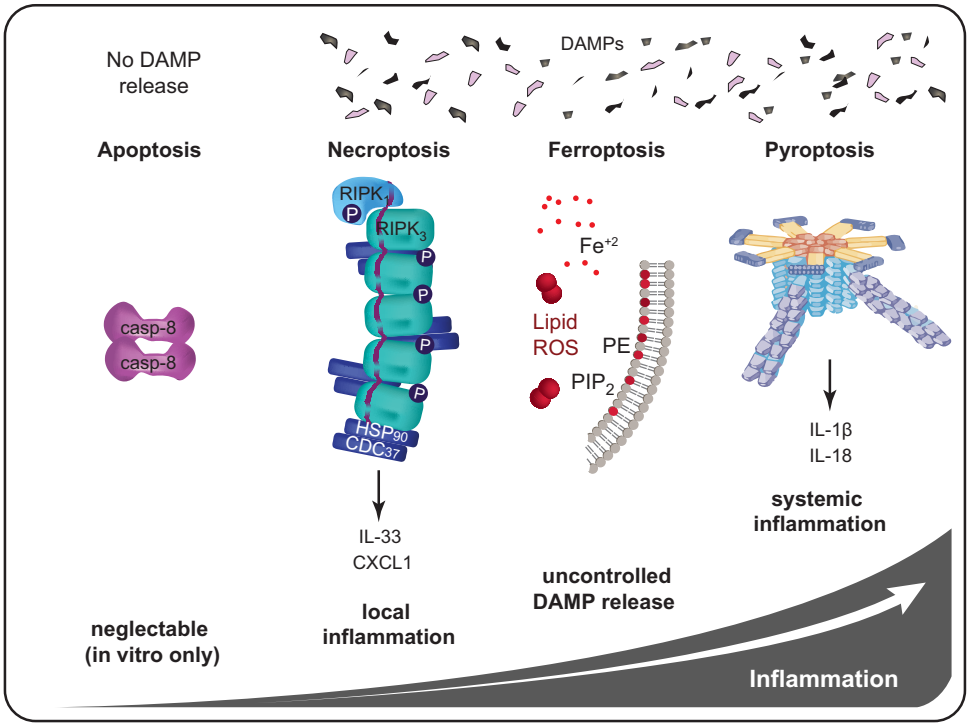



**FIGURE 13.** The hypothetical immunological hierarchy of regulated cell death (RCD) pathways. The current model of necroinflammation ascribes the most potent systemic inflammatory trigger to pyroptosis, because it adds IL-1$\beta$ and IL-18 release on top of classical DAMP release. Therefore, pyroptosis is the most potent known trigger of the immune system. In contrast, apoptosis results in neglectable inflammation only, a very local process that involves the uptake of apoptotic bodies by macrophages. Artificial conditions are required for apoptosis to exhibit any long-lasting stimulation of the immune system, given the absence of DAMP release. In ferroptosis, no modulation of the immune system has been described so far apart from the release of DAMPs in contrast to necroptosis, during which IL-33 and CXCL-1 are actively produced to inhibit the immune response by *1*) stabilization of regulatory T cells and *2*) inhibition of infiltrating NK cells, respectively.

Viral infections are classically cleared by induction of apoptosis in infected cells. Obviously, systemic infection is not a favorable condition to defend viruses. However, upon viral expression of caspase inhibitors, it takes necroptosis to control the virus. In this scenario, DAMPs are being released, but in parallel anti-inflammatory cytokines are produced. Therefore, necroptosis contains "anti-inflammatory" components. Examples are IL-33, which stabilizes regulatory T cells in the microenvironment, and CXCL1, which directly inhibits natural killer cells.

As far as we understand the pathway of ferroptosis while this review was written, no modifications of the immune system by cells that die by ferroptosis have been described. Therefore, this RN pathway appears to represent an example of DAMP release by plasma membrane rupture in the prototypic sense.

Some conditions require more involvement of the immune system than simply releasing DAMPs. Whenever cells die by pyroptosis, long-lasting proinflammatory cytokines are actively matured by the same machinery that cleaves gasdermin D. IL-1$\beta$ and IL-18 reach high intracellular concentrations before plasma membrane rupture finally releases these factors. The consequences to the organism are systemic inflammation, acute phase response, and fever.

Lastly, the subroutine of regulated cell death, through the specific release of defined DAMPs, determines the regenerative response in an organ specific manner.

## VII. ROLE OF DAMPs IN REGENERATION FOLLOWING NECROTIC INJURY

### A. General Aspects on Regeneration Following Necrotic Injury

A possible role of DAMPs in regeneration was already mentioned in the 2003 article where these molecules were described for the first time. Land (336) proposed: "Like the insult of ischemia-reperfusion, other risk factors have been implicated in long-term renal allograft dysfunction. . . . Each of these may cause induction of HSPs that interact with TLRs on donor vascular cells. . . . An inflammatory milieu is created in the arterial wall that results in subintimal differentiation and proliferation of smooth muscle cells, as well as in the induction of fibrogenic processes." Today it has become clear that regeneration following cell/tissue injury is a classical intrinsic process of the innate immune system where numerous DAMP-activated PRR-bearing cells instigate, modulate, and orchestrate repairing pathways in a sequence of steps by promoting cellular crosstalk and secretion of signaling molecules, including cytokines, chemokines, and growth factors.

A variety of hematopoietic and nonhematopoietic cells of the innate immune system are regarded as the key regulators of tissue repair and regeneration (696). These PRR-bearing cells include mobile inflammatory monocytes and tissue-resident macrophages (432, 608, 697) as well as fibroblasts/myofibroblasts (3117, 313, 442), vascular cells including bone marrow-derived endothelial progenitor cells (233,

522, 557, 675), epithelial cells such as keratinocytes (515) and tubular cells (231), hepatic stellate cells (681), and, last but not least, stem cells, particularly mesenchymal stem cells (MSCs) (123, 253).

Once activated, all these members of the large family of innate immune cells become involved in resolving inflammation, repairing damaged tissue immediately after tissue damage. Theoretically, all these cells expressing PRRs may be activated by DAMPs and, indeed, for some of them, this has already been shown. Orchestrating the first step of regeneration, the highly organized phagocyte-mediated resolution of innate immune inflammation, DAMPs drive the mechanism of efferocytosis as critical processes in efficient clearance of cellular debris and dead cells by phagocytes (14).

Another example refers to the observation that the DAMP fibronectin extra domain A, through TLR signaling, is a potent stimulus for collagen production, myofibroblast differentiation, and wound healing in vitro (49). Further examples point to the role of HMGB1 in the differentiation of lung fibroblasts into myofibroblasts and enhanced cell migration (359) to promote 3T3 fibroblast wound healing by inducing cell proliferation and migration (536), to enhance proliferation of pulmonary arterial smooth muscle cells and human arterial endothelial cells (722), and to activate fibrogenic hepatic stellate cells in vitro (286).

Moreover, DAMPs were found to activate circulating bone marrow-derived stromal stem cells which facilitate the repair processes. Thus DAMPs were demonstrated to promote both proliferation and trafficking of MSCs, identifying HMGB1 as a key factor in the regulation of these processes (395, 511, 520). Other DAMPs, namely 100A4 proteins and uric acid, have dose-dependently been shown to induce chemotaxis of MSCs with synergistic effects when combined (149). In this context, it is worth mentioning the process of autophagy that plays an essential role in regulating cell viability during tissue repair (140). Once again, autophagy is triggered and regulated by DAMPs (243, 367).

Together, there is increasing evidence indicating a crucial role for DAMPs in repair and regeneration. Since HMGB1 and eATP represent the most investigated DAMPs in this blooming field of regeneration mechanisms [as also reviewed elsewhere (651)], some more details are added in the following by focusing on the key events of fibrogenesis, angiogenesis, and reepithelialization.

## B. Involvement of HMGB1 in Regeneration

In addition to its promotion of MSCs migration and proliferation (395, 511, 520), HMGB1, in studies on skin grafting, was shown to operate as a chemoattractant by inducing accumulation of bone marrow-derived epithelial progenitors in skin grafts, promoting inflammatory suppression in the grafts, and subsequent epithelial tissue regeneration (615).

Novel insights were gained from the role of DAMP-promoted inflammatory response in myocardial injury, repair, and remodeling (173). For example, in studies on a model of acute myocardial infarction in transgenic mice exhibiting the cardiac-specific overexpression of HMGB1 in cardiomyocytes or local administration of HMGB1 provided first in vivo evidence that this DAMP induces myocardial regeneration by enhancing angiogenesis, restoring cardiac function and improving survival after myocardial infarction (311).

In such studies, murine necrotic myocardial cells and DAMP release, including HMGB1, galectin-3, S100$\beta$, S100A8, and S100A9, were shown to trigger a significant increase in fibroblast proliferation, $\alpha$-smooth muscle actin activation, and collagen 1A1 and 3A1 mRNA expression and to significantly increase fibroblast motility in a cell-wounding assay in a TLR4- and RAGE-dependent manner (736). The profibrogenic role of HMGB1 could also be demonstrated in a study on a model of liver fibrogenesis (287). These experiments suggest that HMGB1 dose-dependently stimulates proliferation of hepatic stellate cells, upregulated de novo synthesis of collagen type I and $\alpha$-smooth muscle actin, and triggered Smad2 phosphorylation and its nuclear translocation through a transforming growth factor (TGF)-$\beta$1-independent mechanism.

In addition to contributing to fibrogenesis, HMGB1 was found to promote angiogenesis. As previously reviewed (708), numerous studies have identified HMGB1 as a critical proangiogenic factor (82, 449) that may potently stimulate endothelial cells (645b), especially upon hypoxic conditions (66). Accordingly, a recent report, again from studies on transgenic mice, shows that heart-specific HMGB1 expression promotes angiogenesis and may reduce the size of myocardial infarction by directly affecting cells from bone marrow (475). Recent experiments also provided evidence for a role of HMGB1 in renal tissue regeneration. As also demonstrated in studies on prostate tumor cells (742), HMGB1 induces activation of the chaperone-like protein clusterin (Clu) that in other sets of studies on Clu knockout mice was shown to be required for renal tissue regeneration in the kidney repair phase after IRI, associated with promotion of tubular cell proliferation (483) and fibrogenesis (219).

## C. Involvement of ATP and Other Nucleotides in Regeneration

There is increasing evidence suggesting that nucleotides, acting as "hybrid DAMPs" ( class Ib/ II DAMPs), actively participate in the three phases of regeneration. The direct

binding to purinergic receptors contributes to this phenomenon, especially the involvement in resolution of inflammation, proliferation of cells, and reepithelialization processes. Two families of P2Rs appear to function in a distinct manner: P2XRs are involved in defense mechanisms and cell death, whereas P2YRs participate in regeneration in response to wounding (254). For example, ATP/UTP released from apoptotic and pyroptotic cells may act as "find-me" signals for macrophages via P2Y2R (152). Human neutrophils, also involved in the resolution phase, were found to release ATP that in turn guides their chemotaxis by feedback through P2Y2 receptors (93). In addition, activation of P2Y2 receptor leads to the actin-binding protein filamin A that participates in the anchoring of membrane proteins for the actin cytoskeleton (719). Furthermore, stimulation of P2YRs by nucleotides revealed mitogenic effects on cardiac endothelial cells (563) and fibroblasts (264). Moreover, as recently reported, uridine adenosine tetraphosphate, a dinucleotide, may function as a proangiogenic factor (746). Taken together, these findings provide evidence for a role of nucleotides as pro-angiogenic DAMPs in tissue repair and angiogenesis.

Nucleotide release during acute renal failure was found to promote tubular cell proliferation (473). Along similar lines, hepatic ATP promotes liver regeneration (214). A more recent report provided evidence for an early release by degenerating neurons of ATP that contributes to the activation of a series of intracellular pathways within Schwann cells that are crucial for nerve regeneration ($Ca^{2+}$, cAMP, ERK1/2, and CREB) (479). As concluded by the authors, these results contribute to define the cross-talk taking place among degenerating nerve terminals and perisynaptic Schwann cells, involved in the functional recovery of the neuromuscular junctions.

ATP acting as a class II DAMP may also contribute to tissue repair via profibrotic pathways mediated by the activation of the NLRP3 inflammasome (see above). Indeed, studies on fibroblasts and different organs have demonstrated that the innate immune sensor NLRP3, mostly inflammasome dependent (18, 292) but also inflammasome independent (672), plays a crucial role in fibrogenesis and can orchestrate profibrotic innate immune responses under both infectious and sterile conditions. In fact, a large body of evidence suggests that the key products of the NLRP3 inflammasome, IL-1$\beta$ and IL-18, exert profibrotic activities, probably secondary to pyroptosis (58, 81, 171, 199, 544). On the other hand, these reports are not without conflicts. For example, more recent studies on lung and dermal fibroblasts resulted in the conflicting observation that IL-1$\beta$ attenuates myofibroblast formation and extracellular matrix production in fibroblasts exposed to TGF-$\beta$1 (439). According to the authors' conclusion, these findings should give rise to reconsideration of the role of IL-1$\beta$ in fibrosis. Thus, to date, the signaling pathways from the inflammasome to myofibroblast differentiation and chronic collagen synthesis have not been fully elucidated and await further clarification (19). It is clear, however, that eATP, when activating P2X7 receptors, promotes inflammation and fibrosis, likely as a consequence of inflammation rather than primary fibrosis (543).

### D. Conclusions

In conclusion, HMGB1 released by injured cells enhances tissue repair by promoting fibrogenesis, angiogenesis, and reepithelialization. In fact, to denote HMGB1 as a prototypic DAMP responsible for regeneration may alone be already supported by the observation that nonprofessional marathon running leads to an immediate rise in HMGB1 serum concentrations which return to baseline levels during a recovery week (40).

## VIII. PERSPECTIVES FOR CANCER AND TRANSPLANT SCIENTISTS

### A. Perspectives for Oncologists

While DAMPs are still living in the shadow in transplant medicine, they have already reached clinical reality in oncology. Growing evidence indicates that expression of DAMPs may have a prognostic or predictive value for cancer patients (177). For example, high CALR levels in malignant cells have been correlated with favorable disease outcome in neuroblastoma patients, pointing to a novel independent prognostic factor (246). Similar results were obtained in lung cancer and ovarian cancer patients treated with ICD inducers such as radiotherapy and paclitaxel, respectively (191). In addition, elevated levels of HSP90 and CALR on the surface of neoplastic cells were shown to be associated with clinical responses among patients with indolent non-Hodgkin's lymphoma recurrence treated with an autologous cancer cell-based vaccine (727). Furthermore, increased concentrations of soluble HSP90 have been detected in the serum of colorectal cancer patients as compared with healthy individuals. The appearance of this DAMP in its soluble form activates cancer cell-intrinsic signaling pathways that promote disease progression (89, 92). Clinical data have shown total CALR levels to be positively associated with accelerated disease progression and poor outcome in gastric cancer patients (86), women with breast carcinoma upon surgery (155), neuroblastoma, bladder carcinoma, and non-Hodgkin's lymphoma patients, irrespective of treatment type (80). In the field of future ICD/DAMPs-based therapeutic anticancer strategies, identifying novel ICD inducers as well as measures that convert non-immunogenic RCD into bona fide ICD is of utmost primordial importance. Indeed, preliminary clinical findings have provided promising evidence that agents that promote emission of CALR, ATP, and HMGB1 as well as secretion

of type I IFN may considerably improve the clinical profile of conventional therapeutic regimens (48). The final goal here is to detect and develop novel therapeutic regimens, for example, using certain combinational approaches, that trigger ICD in a way able to destroy every tumor in every patient. Speculatively, particular cycles of chemotherapy could target specific forms of RCD as ICD, thus additionally preventing resistances to treatment.

### B. Perspectives for Transplantologists

The discovery made by oncoimmunologists that a given injury must initially induce an oxidative/ER stress response that proceeds to subsequent spatiotemporally coordinated emission of distinct DAMPs in the course of RCD to elicit a robust anti-tumor immune response is of outmost importance for transplantologists. Of note, from the perspective of this review, a large body of evidence now emphasizes that the "head of the snake" to induce adaptive immunity has to be seen in the action of ROS which in both scenarios, IRI-induced allograft rejection and ICD inducer-promoted tumor rejection, operate at the front line. Moreover, since these oncoimmunological observations are reminiscent of similar stress responses and ways of DAMP emissions as those found in experimental and clinical settings of IRI, a paramount question needs to be addressed: Is there a universal principle underlying all injury-induced stress responses? If necroinflammation was to define the innate and adaptive immune responses through a specific DAMP signature, this could explain the hierarchically and spatiotemporally orchestrated "collaboration axis" between various classes of DAMPs. Such signatures would fine-tune an adaptive immune response against dead cell-associated antigens. This question and other recent contributions from oncoimmunologists to the concept of injury-induced immunity may encourage transplant researchers to redesign experimental and clinical studies dedicated to this paradigm shift in immunology. It is possible that such findings from work in the field of oncoimmunology will stimulate research on mechanisms of injury-induced allograft rejection. For example, transplant immunologists can promote experiments on allograft IRI or donor brain death models aimed at exploring distinct initial stress responses and peculiar ways of intragraft cell death. This may help to explore an "allo-ICD" as compared with an ICD in cancer. At least the four therapy-induced mandatory factors promoting tumor ICD (CALR, eATP, HMGB1, and type I IFN/CXCL10) have been shown to be implicated in IRI as well (84, 174, 255, 617, 636, 639, 698) (compare **FIGURE 11**).

Another approach to allotolerance induction, achieved in the absence of injury, might lie in the validation of anecdotal studies on the administration of highly purified (ultracentrifuged) xenogeneic proteins (gammaglobulins) that were shown to successfully induce tolerance in mice, dogs, and humans (60, 137, 339). In pursuing this principle of tolerance induction by using a soluble, partially purified fraction of histocompatibility (H)-2a antigen, induction of specific tolerance of humoral-antibody formation was observed in mice injected with this soluble antigen since birth; however, cell-mediated immunity, as measured by skin graft survival, remained intact (356). Although these early observations were only partially successful, newer refined methods for optimal purification of histocompatibility antigens may justify the conduction of similar studies using escalating doses of highly purified HLA antigens.

Accumulating data indicate that 1) tumor cells can convert specific DC subsets into regulatory ("tolerogenic") DCs that stimulate Treg cell proliferation, and 2) tumor microenvironment can alter myeloid cells by converting them into MDSCs that are an important component of a cancer-induced immunosuppressive milieu (290, 564, 687). Future research efforts in this regard appear to be well justifiable (429). Provided the cell death targeting strategies and the associated lack of DAMP release, any transplantation-associated allograft injury and its early consequences should be preventable, at least that is the theory.

To generate a successful allotolerance induction, experiments should especially be designed to allow presentation of alloantigens under subimmunogenic conditions in an undamaged noninflammatory microenvironment. This concept has already been successfully applied in a murine model of tolerance induction to the single immunodominant class II MHC-presented male (HY) peptide (653). Finally, when methods to prevent the initial allograft injury fail or are insufficient, transplant researchers could strive for exploring a potential role of RN and DAMP-induced stress responses such as UPR and DDR in allografts exposed to injuries such as IRI. Such studies may pave the way to identify molecules involved in UPR and DDR as new targets for innovative immunosuppressive therapy. The transient use of inhibitors directed against RN and/or selected classes of DAMPs, during the time when an allograft is exposed to an injury, is an effective treatment to prevent allograft rejection including antibody-mediated rejection. We predict that such therapeutic approaches would ideally include combinational use of inhibitors preventing the release of DAMPs from cells that undergo RN (380). In this context, ferroptosis might be of special interest for kidney and liver transplantation.

## IX. SUMMARY ON ORIGIN AND CONSEQUENCES OF NECROINFLAMMATION

In summary, the different facets of necroinflammation appear to depend on the type of necrosis that induces it and on the perception of this complex signal by the cells that are located next to the damage. While all RN pathways release a general pattern of DAMPs, including entire broken organ-

elles, necroptosis, ferroptosis, and pyroptosis clearly release additional specific DAMP patterns. This allows particular fine tuning of the definite DAMP profile and may explain why several signaling pathways of necrosis are encoded in the genome. However, it has still not been ruled out completely that regulated necrosis actually is of importance during development. As recently discovered, salivary gland cells in *Drosophila melanogaster* undergo caspase-independent cell death during normal development with a clear implication on the immune response (377). Strictly following the nomenclature of cell death, such a pathway should be referred to as programmed necrosis (182).

From a clinical perspective, many implications of necroinflammation are important. In the case of cancer, this may shape the tumor microenvironment, and research on necroinflammation may provide insights into cancer immunotherapy. In transplantation, necroinflammation that may be triggered by ischemia-reperfusion injury should be avoided. Similarly, necrotic tissues in hypoxic brain and heart may trigger detrimental organ swelling and arrhythmias. Necrosis in several settings of intoxications also is associated with a significant immune infiltration. Lastly, autoimmunity may be strongly initiated following failure to remove necrotic tissue. This might explain the increased likelihood for an acute autoimmune episode following viral/bacterial infections that are cleared by necrosis. We conclude that a better understanding of necroinflammation as a therapeutic target is urgently awaited.

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## DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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