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Comprehensive Review

Transplantation and Damage-Associated Molecular Patterns (DAMPs)

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Upon solid organ transplantation and during cancer immunotherapy, cellular stress responses result in the release of damage-associated molecular patterns (DAMPs). The various cellular stresses have been characterized in detail over the last decades, but a unifying classification based on clinically important aspects is lacking. Here, we provide an in-depth review of the most recent literature along with a unifying concept of the danger/injury model, suggest a classification of DAMPs, and review the recently elaborated mechanisms that result in the emission of such factors. We further point out the differences in DAMP responses including the release following a heat shock pattern, endoplasmic reticulum stress, DNA damage-mediated DAMP release, and discuss the diverse pathways of regulated necrosis in this respect. The understanding of various forms of DAMPs and the consequences of their different release patterns are prerequisite to associate serum markers of cellular stresses with clinical outcomes.

Abbreviations: ACD, accidental cell death; AIM2, absent in melanoma 2; ALRs, absent in melanoma 2 (AIM2)-like receptors; alum, aluminum sulphate; AML, acute myeloid leukemia; ATF6, activating transcription factor 6; BCL2, B-cell CLL/lymphoma 2; BD, brain death; BECN1, beclin 1; CALR, calreticulin; CCR7, C-C chemokine receptor type 7; CXCL10, chemokine (C-X-C motif) ligand 10; CXCR3, CXC chemokine receptor 3; Cyt, cytochrome c; DAMPs, damage-associated molecular patterns, danger-associated molecular patterns; DC, dendritic cell; DDR, DNA damage response; dsDNA, double-stranded DNA; dsRNA, double-stranded RNA; eATP, extracellular adenosine triphosphate; e^-, electrons; ERAD, ER-associated degradation; ER, endoplasmic reticulum; FADH2, flavin adenine dinucleotide (reduced form); Foxp3, forkhead-box-protein P3; GSDMD, gasdermin D; GVHD, graft-versus-host disease; HMGB1, high-mobility group box 1; HSFs, heat shock transcription factors; HSPs, heat shock proteins; HSR, heat shock response; HY, male-specific; ICD, immunogenic cell death; IFNAR1/2, interferon (alpha, beta, and omega) receptor 1/2; IFNs, interferons; IFN-γ, interferon-gamma; IRE1, inositol-requiring enzyme 1; IRF3, interferon regulatory factor 3; IRF, interferon regulatory factor; IRI, postischemic reperfusion injury; MICA/B, MHC class I chain-related proteins A and B; MSU, monosodium urate; NADH, nicotinamide adenine dinucleotide (reduced form); NDV, Newcastle disease virus; NETs, neutrophil extracellular traps; NK cells, natural killer cells; NKG2D, natural killer group 2, member D protein; NLRP3, NOD-like receptor family, pyrin domain containing 3; NLRs, nucleotide-binding oligomerization domain (NOD) and leucine-rich repeat receptors; $O2^{-\bullet}$, superoxide anions; P2X7R, purinergic P2X 7receptor; P2X, purinoceptor 7; PAMPs, pathogen-associated molecular patterns; PERK, protein kinase R (PKR)-like endoplasmic reticulum kinase; PRRs, pattern recognition receptors; Q, coenzyme Q; RAET1, gene cluster retinoic acid early transcripts 1; RCD, regulated cell death; RHIM, RIP homotypic interacting motif; RIPK, receptor-interacting protein kinase; RN, regulated necrosis; ROS, reactive oxygen species; STING, stimulator of interferon genes; TLRs, Toll-like receptors; TRPV, transient receptor potential vanilloid; TXNIP, thioredoxin-interacting protein; ULBPs, UL-16 binding proteins; UPR, unfolded protein response

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The Danger/Injury Model in Immunology

Twenty years ago the danger/injury model in immunology was formulated and published, holding that the immune

system does not care about self and non-self, but that it is any form of cell stress/tissue injury rather than the presence of non-self that induces immunity. The model emerged from two sources: (i) its publication by the Munich transplant group on the basis of significant data from a clinical trial in transplant patients, providing compelling evidence that tissue injury (here: allograft injury) induces immunity (here: alloimmunity-mediated allograft rejection) (1); (ii) its description by Polly Matzinger in the form of a self-coherent chain of argumentation on theoretical grounds resulting in the stringent conclusion that the "self/non-self" discrimination theory of immune responses is inappropriate (2). After the (re)discovery of the innate immune system, the model was modified by the two groups and currently holds that any cell stress, any tissue injury, even the slightest intra- or extracellular perturbation of the microenvironment activate the innate immune system, which reacts with an inflammatory response that, in the presence of "non-self" or "altered-self" antigens (or even "self"), elicits a specific adaptive immune response. The core of the danger/injury model refers to the generation of damage-associated molecular patterns (DAMPs), a term coined in the early 2000s (3,4), and also denoted as "danger signals" in the international literature. In fact, uric acid was identified as a danger signal in 2003 (5), which was subsequently accepted as a true nonbacterial DAMP (6).

DAMPs are endogenous molecules that are emitted under various conditions of major cell stress or tissue injury. In analogy to pathogen-associated molecular patterns (PAMPs), DAMPs are sensed by either "classical" pattern recognition receptors (PRRs) or "non-classical" receptors found on the surface or within the cells of the innate immune system (referring to both mobile immune and sessile nonimmune cells), thereby leading to their activation. DAMPs are (1) exposed on the plasma membrane of stressed cells, or (2) actively secreted by stressed cells or cells at an early stage of apoptosis, or (3) passively released into the extracellular environment from dying plasma membrane-ruptured cells, or (4) released from the damaged extracellular matrix (7–9). Importantly, DAMPs also include "homeostatic danger signals," that is, danger signals that do not derive directly from dying cells but are associated with perturbations of tissue/cell homeostasis and may signal pathological stress (10).

In the field of organ transplantation, the danger/injury model was tackled for the first time in the early 2000s (11–15) and, more recently, comprehensively addressed in a monograph (16). According to currently accepted models (9,16–30), any injury to an allograft, in particular, the "canonical" oxidative injury as occurring in the donor under brain death condition and in the recipient during postischemic reperfusion, leads to induction of various classes of DAMPs that activate intragraft PRR-bearing cells of the donor's and recipient's innate immune system, a process that results in inflammation of the allograft. In parallel, donor-derived and recipient-derived dendritic cells (DCs), activated after uptake of alloantigens and recognition of various DAMPs by their corresponding PRRs, elicit—via the process of direct and indirect allorecognition—a robust adaptive anti-donor alloimmune response ultimately resulting in allograft rejection (9,16–30).

In this review, we will present a brief overview about the initial oxidative allograft injury that represents the true point of origin of DAMP emission via instigation of stress responses and induction of cell death. We then attempt to provisionally classify DAMPs by briefly touching on their role in the activation of immunostimulatory DCs able to prime naïve $CD4^+$- and $CD8^+$ T cells. Subsequently, the major sources of their generation and emission, namely, those stress responses and distinct forms of regulated cell death (RCD) such as necroptosis, are highlighted. In a complementary continuative review (31), we will present evidence indicating that the scenario of DAMP-provoked allograft immunogenicity shows a striking mechanistic similarity with DAMP-evoked tumor immunogenicity; a recent understanding in oncoimmunology that has led to new strategies in modern anticancer therapy.

Oxidative Injury to Allografts in the Donor and the Recipient

Allografts are potentially exposed to many injuries starting from conditions in the organ donor, continue during organ preservation and end up with implantation-associated postischemic reperfusion injury (IRI) in the recipient. Consequently, two different innate immune systems, that of the donor and that of the recipient, are activated followed by mounting an intragraft sterile inflammatory response and leading to an adaptive alloimmune response in the recipient.

First severe injury to an allograft occurs already in the organ donor. In particular, development of reactive oxygen species (ROS)–mediated oxidative stress under brain-death (BD) conditions is substantial as demonstrated in both experimental models and deceased organ donors. Together with the scenario of ROS-mediated IRI in the recipient, it may be regarded as the canonical injury an allograft is exposed to.

Donor BD: Oxidative Stress-Mediated Activation of the Innate Immune System

A decade ago, early experiments on a rat model revealed a strong influence of BD condition on chronic graft dysfunction (32). Emerging evidence now indicates that donor BD conditions, associated with oxidative stress (including oxidative stress-induced endoplasmic reticulum

[ER] stress associated with apoptosis) activate the innate immune system, which leads to development of an acute systemic auto-inflammatory syndrome (24,33–39), often associated with the demonstration of an apoptotic signature in cells of removed donor organs (kidney, heart) (38–44).

In fact, documented parameters involved in BD-activated innate immune events include DAMPs (45–47), upregulated PRRs and signaling molecules (46,48,49), complement fragments (50), cytokines such as IL-1β (36,51,52), and upregulated chemokine receptors (18). Moreover, mature activated DCs could also be demonstrated in the blood and spleen of brain-dead organ donors (Table 1) (53,54).

Certainly, these severe systemic innate immune processes occurring under BD conditions can causatively be made responsible, besides IRI, for the well-known phenomenon of delayed graft function of kidneys removed from BD donors (55).

ROS-Mediated Postischemic Reperfusion Injury

The pivotal influence of IRI on acute and chronic rejection events is well known from an early clinical trial in kidney transplant patients conducted 20 years ago (1,16,56). Since that time, the phenomenon of ROS production during IRI has been demonstrated in numerous experiments on various IRI models and also in a clinical study on human renal allografts (9,16,57).

Table 1: Association of brain death condition with parameters of innate immunity

Parameters of innate immunity	"Innate" molecules demonstrated under brain death conditions	References (no.)
Oxidative injury	ROS (indirectly measured)	(33,36)
Complement	C3, C5b-9	(50)
DAMPs	HMGB1, HSP70	(45,47)
PRRs	TLR2, TLR4	(46,48)
Signaling molecules	NF-κB, JNK[1]	(35,44,49)
Cytokines	IL-1β, IL-6, TNF	(36,44,48,51,52)
Chemokine receptors	CxCR1, CxCR2	(18)
Adhesion molecules	ICAM[1]	(18)
Dendritic cells	Mature DCs	(53,54)

CxCR, C–X–C motif receptor; DAMPs, damage-associated molecular patterns; DCs, dendritic cells; HMGB1, high mobility group box 1; HSP70, heat shock protein 70; ICAM, intracellular adhesion molecule 1; JNK, c-Jun NH(2)-terminal kinase; NF-κB, nuclear factor kappaB; PRRs, pattern recognition receptors; ROS, reactive oxygen species; TLR, Toll-like receptor; TNF, tumor necrosis factor.
[1]Demonstrated in experimental models of brain death only.

Regarding mechanisms of ROS generation in IRI, it is generally acknowledged that its production during the very first minutes of reperfusion is provided by vascular cells (in the allograft setting, donor-derived) (16,58).The second burst of ROS production in the course of IRI is thought to originate from phagocytic cells (in the allograft setting, recipient-derived), that is, polymorphonuclear neutrophils and macrophages that enter the reperfused tissue, adhere to the endothelium, and get activated under the influence of ROS initially produced by vascular cells.

There is a variety of different sources of ROS; however, according to most studies, the accelerated and excessive ROS production in postischemic tissues is due to the activity of enzymes that are capable of reducing molecular oxygen to form superoxide ($O_2^{-\bullet}$) and/or hydrogen peroxide, with the subsequent release of ROS into the intracellular and/or extracellular compartments. These enzymes include three hypoxia-sensing systems, that is, the mitochondrial electron transport chain–associated enzymes (mainly through complex I and III), xanthine oxidase, and reduced form of *nicotinamide adenine dinucleotide phosphate* oxidases as well as uncoupled nitric oxide synthase. Several mechanisms have been shown to contribute to ROS production, but hypoxia/hypoxic periods seem to play a dominant role in the activation of these ROS-producing enzyme systems that are able to sense oxygen tension (16,59–72). In fact, one of the notions in oxidative stress research, namely, that hypoxia-sensing enzyme systems contribute to the production of ROS, can easily be applied to transplant settings where notoriously hypoxia-damaged donor organs are used (Figure 1) (9,71).

The evolution of the concept of ROS-mediated IRI as well as the cell biology involved in IRI have recently been reviewed, in particular, by addressing the consequences of IRI including but not limited to elicitation of cellular stress responses such as the unfolded protein response (UPR) and DNA damage response (DDR) as well as the induction of cell death subtypes in terms of RCD and accidental cell death (ACD) (21,72–77). Since these topics have recently taken center stage in the research field of stress responses → RCD → immunity, they will be detailed below. In particular, the impact of IRI on necroptosis, parthanatos, and (more pronounced) ferroptosis (21,78–81), ER stress/UPR (78,82–90), ER stress/UPR/autophagy (82,83,91–102), and DDR (103–112) has recently been highlighted. These reports clearly attest IRI to be critically implicated in the emission of a plethora of DAMPs inherently capable—via recognition by PRRs on/in cells of the innate immune system—to instigate various inflammatory and adaptive immune pathways promoting, for example, acute and chronic allograft rejection.

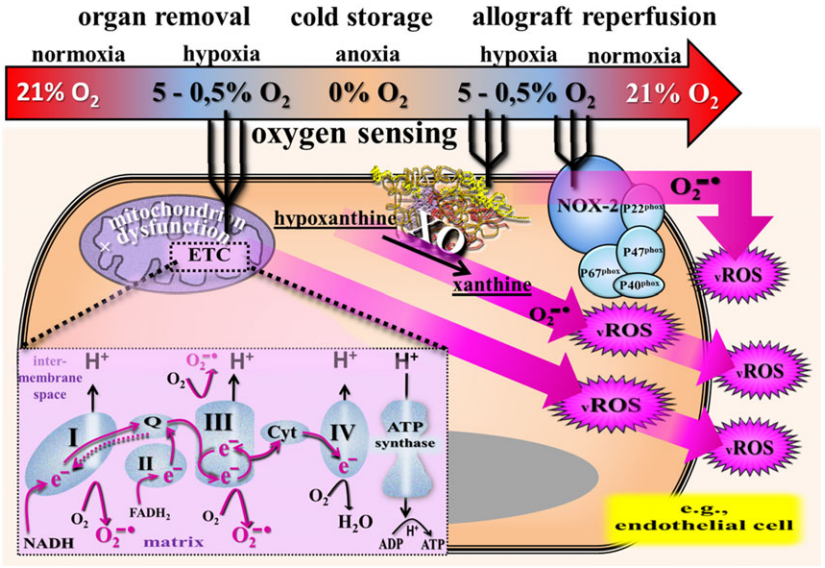


Figure 1: Simplified scenario model of hypoxia-induced ROS generation by allograft vascular cells. Low oxygen contents at hypoxic phases during organ removal and implantation are sensed by three enzyme systems located in vascular cells of the donor organ (i.e. the mitochondrial respiratory chain as well as the two oxidase enzyme systems). In case of reperfusion, the restored tissue O_2 reacts with hypoxanthine and XO to generate xanthine and superoxide anions (and hydrogen peroxide, not shown here). In addition, upon cell activation via hypoxia-HIF-1α (not shown here), the critical protein subunits of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system (e.g. $p47^{phox}$, $p40^{phox}$, and $p67^{phox}$) translocate to the cell membrane where they dock with the NOX-2 and $p22^{phox}$ homolog. The fully assembled enzyme then generates superoxide via one-electron reduction of molecular oxygen using cytoplasmic NADPH as an electron donor. Moreover, ROS is produced by the ETC in the course of hypoxia and/or mitochondrial dysfunction. It takes place in the mitochondrial membranes. During this scenario, the hydrogen protons (or a pair of electrons) are transported from one carrier to another and they are finally used to reduce oxygen to water. During this transfer of electrons, a lot of energy in the form of ATP is released. ADP, adenosine diphosphate; ATP, adenosine triphosphate; Cyt, cytochrome c; e^-, electrons; ETC, electron transport chain; $FADH_2$, flavin adenine dinucleotide(reduced form); H^+, hydrogen proton; NADH, nicotinamide adenine dinucleotide (reduced form); $O_2^{-\bullet}$, superoxide anions; Q, coenzyme Q; ROS, reactive oxygen species; XO, xanthine oxidase.

A Plethora of DAMPs and an Attempt to Classify Them

During the past decade, a large variety of DAMPs generated from various sources and emitted during various injurious scenarios have been discovered. Table 2 summarizes some selected most prominent DAMPs characterized to date in studies on cell death/tissue injury settings including IRI and tumor models as well as their mode of emission (5,9,16,30,113–209). In view of such a plethora of DAMPs, several reasonable approaches to classify them have been reported (7,10,210,211). Nevertheless, the nomenclature of DAMPs in the literature is still confusing. Thus, for this article only and with focus on their crucial role in allograft rejection, they are didactically divided into six classes (Ia/Ib, II, III, IV, and V). Of course, this approach is debatable and we freely admit that there are still some deficits in our classification waiting for a final resolution (Table 3). Notwithstanding, there is compelling evidence suggesting that all six DAMP classes can promote the generation of immunostimulatory DCs by either directly triggering signaling pathways in DCs or activating other cellular/humoral innate immune processes that indirectly contribute to DC maturation. A few examples are briefly sketched in the following discussions.

Class Ia/Ib DAMPs

According to this classification, molecules such as the nuclear protein *high mobility group box 1* (HMGB1), heat shock proteins (HSPs), S100 proteins, nucleic acids, or proteoglycans are denoted as class Ia DAMPs because they are directly sensed via binding to a variety of PRRs on/in cells of the innate immune system. These "classical" PRRs include Toll-like receptors (TLRs), C-type lectin receptors, *nucleotide-binding oligomerization domain (NOD) leucine-rich repeat* receptors (NLRs), *retinoic acid-inducible gene 1–like* receptors, and *absent in melanoma 2* (AIM2)-like receptors (ALRs), and *interferon-inducible p200 family* proteins (180,184,212–220).

Class Ia DAMPs such as HMGB1 and HSPs are generated in reperfusion-injured organs including human renal allografts (9,16,45,148–150,212–232), but also emitted under BD conditions (46,47,233–236). These molecules considerably contribute to creation of sterile inflammation including IRI-mediated inflammation when sensed by

Table 2: A list of prominent damage-associated molecular patterns (DAMPs) associated with cell stress/cell death and/or tissue injury (selected and in alphabetical order)

DAMP	Mode of emission	Cognate receptor	Reference (no.)
Adenosine triphosphate (ATP)	Mostly passively released; sometimes actively secreted	P2Y2; P2X7; (indirectly: NLRP3)	(9,113–122)
Biglycan (BGN)	Extracellular matrix	TLR2, TLR4, P2X4, P2X7	(123–125)
Calreticulin (CALR)	Mostly surface exposed; sometimes passively released	CD91	(117,126–131)
Fibrinogen	Extracellular matrix	TLR4	(124,132)
Fibronectin extra domain A	Extracellular matrix	TLR4?	(124,133)
Heat shock proteins HSP70/72, HSP90, HSP60	Surface exposed; actively secreted; passively released	TLR2, TLR4, CD91, SREC-1, FEEL-1	(9,10,134–142)
Heparan sulfate fragments	Extracellular matrix	TLR4	(124,143)
High-mobility group box 1 (HMGB1)	Mostly passively released; sometimes actively secreted	TLR2, TLR4, RAGE, TIM3	(9,141,144–150)
Hyaluronan fragments (fHA)	Extracellular matrix	TLR2, TLR4, NLRP3?	(9,124,142,151–156)
MHC class I chain-related proteins (MICs)	Surface exposed	NKG2D	(9,157–165)
Monosodium urate (MSU) or uric acid	Passively released	Purinergic receptors (indirect: NLRP3)	(5,113,122,166–170)
Nonmuscle myosin II-A heavy chain (NMHC-II)	Surface exposed	Pre-existing natural IgM antibodies	(9,171,172)
Nucleic acids (RNA, cytDNA, mtDNA)	Passively released (e.g. from nucleus, mitochondria, cytosol)	TLR3, TLR7, TLR9, RIG-I, AIM2, cGAS,	(30,141,142,173–191)
Oxidation-specific molecules/epitopes	Passively released	CD36, SR-A, TLR2/4, CD14, natural IgM antibodies	(192–197)
S100 proteins (e.g. S100 A1/8/9/12)	Passively released	RAGE, TLR4	(142,167,198–203)
Tenascin	Extracellular matrix	TLR4	(204,205)
UL16 binding proteins (ULBPs)	Surface exposed	NKG2D	(206–208)
Histone	Passively released (from nucleus)	TLR9	(209)

AIM2, absent in melanoma 2; CD, cluster of differentiation; cGAS, cyclic GMP-AMP synthase; cytDNA, cytosolic DNA; FEEL-1, fasciclin epidermal growth factor–like/common lymphatic endothelial and vascular endothelial receptor-1; mtDNA, mitochondrial DNA; NKG2D, natural-killer group 2, member D; NLRP3, NLR family, pyrin domain-containing protein 3; P2X7, purinergic P2X7 receptor; P2Y2, purinergic P2Y2 receptor; RAGE, receptor for advanced glycation end products; RIG-I, retinoic acid inducible gene I; SREC-1, scavenger receptor class f member 1; TIM, transmembrane immunoglobulin and mucin domain; TLR, toll-like receptor.

those members of the NLR or ALR family that form inflammasomes (120,122,237–241). These cytosolic multiprotein platforms orchestrate innate immune defense responses to infectious or sterile insults through engagement with caspase-1 activation, to catalyze proteolytic cleavage of pro-interleukin-1β (pro-IL-1β) and pro-IL-18 to their mature bioactive forms (120,122,237–239). In addition, in case of severe insults, this process can drive pyroptosis, an inflammatory form of RCD (237,239) (Figure 2). There is increasing evidence indicating that two prominent members of the inflammasome family *NOD-like receptor family, pyrin domain containing 3* (NLRP3) and to a lesser degree AIM2, play important roles as sensors of DAMPs (120,122,240–248). However, their activation mechanisms are different in that activation of the canonical NLRP3 inflammasome in macrophages requires two signals, a "priming" and a second activating signal (Figure 2).

Of note, class Ia DAMPs, such as HMGB1, HSPs, and nucleic acids, have been shown to promote DC maturation. For example, as demonstrated in various lines of studies, HMGB1 and members of the HSP70 family, via recognition by TLRs and the receptor of advanced glycation end products, promote maturation of immunostimulatory DCs, thereby favoring the proliferation and the Th1 polarization of T cells (249–256).

Besides these "classical" PRRs, some other innate immune recognition receptors have been described including "nonclassical" receptors such as the scavenger receptor low-density lipoprotein receptor–related protein 1 (LRP1, best known as CD91) binding, for example, to calreticulin (CALR) (129,257) as well as the purinergic receptors binding to extracellular adenosine triphosphate (eATP) and uric acid (monosodium urate [MSU]) (119,122), here denoted as class Ib DAMPs. This family

Table 3: Classification of DAMPs according to their capacity to activate dendritic cells[1]

Classes of DAMPs[1]	Categories of cognate recognition receptors/sensors (cell-bound, humoral)
Class Ia DAMPs: DAMPs such as HMGB1, HSPs, and nucleic acids including cytosolic DNA	Recognized by classical recognition receptors = pattern recognition receptors = PRRs on/in DCs triggering signaling pathways thereby directly promoting DC maturation (e.g. TLRs, RLRs, ALRs)
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 DC 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 DC activation
Class III DAMPs: DAMPs exposed on stressed cells such as MICs and ULBPs	Recognized by the activating NKG2D receptor on NK cells assisting in DC maturation
Class IV DAMPs: DAMPs in terms of neoantigens/neoepitopes (such as NMHC-II, oxidized phospholipids, actin cytoskeleton, etc.)	Recognized by binding to pre-existing natural IgM antibodies to activate the complement cascade thereby contributing to DC activation
*Class V DAMPs: d*yshomeostasis-*a*ssociated *m*olecular *p*atterns (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 DC activation

ALRs, absent in melanoma 2 (AIM2)-like receptors; CALR, calreticulin; CD, cluster of differentiation; DAMPs, damage-associated molecular patterns; DCs, dendritic cells; eATP, extracellular ATP; ER, endoplasmic reticulum; HMGB1, high-mobility group box 1; HSPs, heat shock proteins; 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; ULBPs, UL16 binding proteins; UPR, unfolded protein response.
[1]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. Of course, this approach is debatable and we freely admit that there are still some deficits in our classification waiting for a final resolution.

of "nonclassical" recognition receptors is not reviewed further here.

Class II DAMPs

The second signal for activation of the canonical NLRP3 inflammasome is provided by PAMPs or another class of DAMPs such as eATP, and MSU that are indirectly sensed without direct binding to NLRP3 to trigger inflammasome assembly, IL-1β/IL-18 release, and pyroptosis (120,239,241,258). They are denoted here as class II DAMPs, which are not only involved in experimental but apparently also in clinical transplantation. For example, the well-known detrimental effects of high uric acid on graft survival may be explained by innate immune mechanisms triggered by this DAMP (259).

Noticeably, there is compelling evidence indicating that ATP is extracellularly released from apoptotic and necrotic cells during IRI (119,260) that, in turn, has been shown in several lines of studies to be implicated in canonical activation of the NLRP3 inflammasome (114,261–265). Recent studies suggest that the purinergic receptor P2X7 and pannexin-1 hemichannels are involved in this process, but the exact mechanism is not quite clear (120,122,241). According to accepted models, eATP primarily binds to the nonclassical receptor P2X7, which is supposed to promote pathways creating an intracellular ion perturbation in form of K^+ efflux and Ca 2^+ influx, thereby reflecting the presence of homeostatic danger signals (10) (denoted as class V DAMPs, see Class V DAMPs) (Figure 2). In this sense, eATP may operate as a "hybrid DAMP." Of note, however, ATP-induced NLRP3 inflammasome activation is differentially regulated between DCs and macrophages (120,122,239,241,242).

Moreover, there is emerging evidence for a role of mitochondria, oxidative stress, and ER stress—in terms of an interrelationship—in the regulation and activation of the NLRP3 complex (120,240,241,243). Like eATP-induced ion perturbations, oxidative stress associated with changes in cellular redox homeostasis can also be regarded as a reflection of homeostatic danger signals sensed by NLRP3 (10). In addition, ER stress and ROS may activate the thioredoxin-interacting protein (TXNIP), besides *apoptosis-associated speck-like protein containing a caspase recruitment domain* (ASC), another adaptor molecule that reportedly associates with NLRP3 to activate the inflammasome complex (120,240,241,243–246). In addition, recent data suggest that gasdermin D (GSDMD), a substrate of caspase-1, is another crucial component of the inflammasome, since its cleavage is required for induction of pyroptosis and secretion of IL-1β (266) (Figure 2), (see RCD: An Efficient Source of DAMP Emission).

In contrast to the complexity of the NLRP3 inflammasome activation, inflammasome activation by AIM2 only depends on the direct recognition of double-stranded DNA (dsDNA). Of note, however, not only microbial DNA

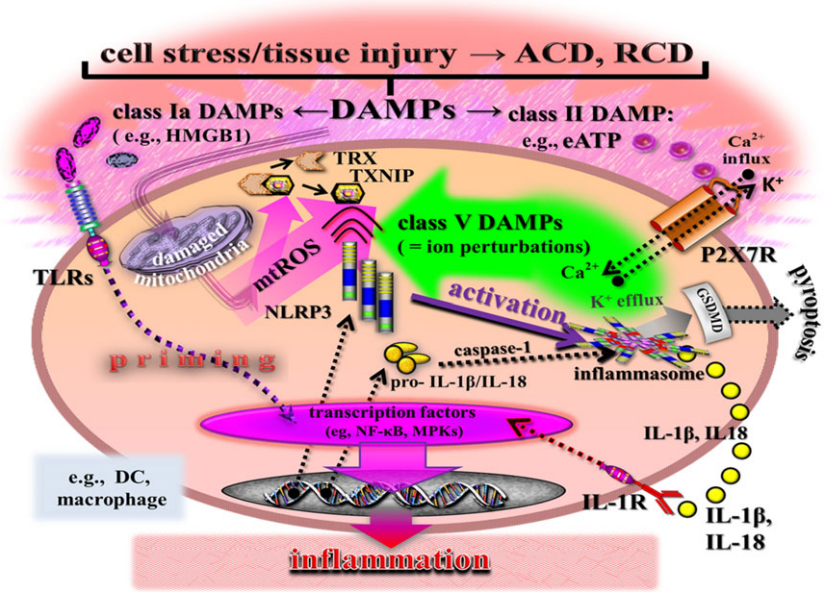


Figure 2: Simplified scenario model of injury-induced activation of the NLRP3 inflammasome. Both class Ia DAMPs ("priming DAMPs" exemplified by HMGB1) and class II DAMPs ("activating DAMPs" exemplified by eATP) are required for NLRP3 inflammasome activation. Class Ia DAMPs are recognized by TLRs, thereby activating transcription pathways (e.g. the NF-kB pathway), leading to upregulation of pro-IL-1β and pro-IL-18 and NLRP3 protein levels. Class II DAMPs such as eATP activate the formation of the NLRP3 inflammasome complex. Under noninfectious conditions, extracellular ATP, primarily, via binding to the P2X7 receptor and purinergic receptor signaling (acting as a "hybrid DAMP"), promotes opening of a central pore allowing for K^+ efflux and Ca^{2+} influx across the membrane. The emerging ion perturbation reflects the presence of class V DAMPs, which are sensed by NLRP3. Dissociated TXNIP, which is triggered by mitochondrial ROS, also contributes to NLRP3 inflammasome activation. Although the exact mechanisms are still unclear, activation of NLRP3 allows inflammasome complex formation and maturation of pro-IL-1β and pro-IL-18 via caspase-1 cleavage to secretion of bioactive IL-1β and IL-18. Then these key cytokines, in an autocrine or paracrine manner, lead to receptor-triggered transcriptional pathways resulting in the production of further proinflammatory mediator substances to create full-scale tissue inflammation. In addition, cleavage of GSDMD, a substrate of caspase-1, is required for pyroptosis (and IL-1β secretion). ACD, accidental cell death, ATP, adenosine triphosphate; K^+, potassium; DAMPs, damage-associated molecular patterns; DC, dendritic cell; GSDMD, gasdermin D; HMGB1, high-mobility group box 1; MPKs, mitogen-activated protein kinases; NLRP3, NOD-like receptor family, pyrin domain containing 3; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; mtROS, mitochondrial reactive oxygen species; P2X7R, P2X purinoceptor 7; RCD, regulated cell death; TLRs, Toll-like receptors; TXNIP, thioredoxin (TRX)-interacting protein.

is under discussion here. There is recent accumulating evidence to suggest that AIM2 also plays an important role in the recognition of self (endogenous) DNA, thereby qualifying AIM2 as a class Ia DAMP-sensing PRR (247,248).

Class III DAMPs

Class III DAMPs refer to induced self molecules on stressed cells that are recognized by activating immune receptors such as natural-killer group 2, member D (NKG2D). NKG2D is expressed on the surface of natural killer cells (NK cells), $CD8^+$ T cells, subsets of $CD4^+$ T cells, invariant NK T cells, and γδ T cells (163–165,267,268). Two families of class III DAMPs, mainly expressed on epithelial and endothelial cells, have been identified in humans: (i) the stress-inducible molecules MHC class I chain–related proteins A and B (MICA and MICB), and (ii) the stress-inducible MHC class I–related molecules, UL16 binding proteins 1, 2, and 3, (ULBPs 1, 2, 3) together with two novel members of this family, the ULBP/retinoic acid early inducible protein 1 (RAET1) gene cluster, ULBP4/RAET1E and ULBP4/RAET1G (163–165,267–271).

Importantly, the upregulation of class III DAMPs on stressed cells promotes activation of NKG2D-bearing NK cells, which are thought to play an important regulatory role by selectively regulating DC functions during the course of immune responses. In addition to the removal of inappropriate DCs, NK cells can also shape adaptive immune responses by promoting DC maturation and influencing the polarization of primary T-cell responses (272,273). For example, NK cells are reportedly implicated in contributing to both cellular and antibody-mediated allograft rejection (274,275).

Interestingly, studies on murine models of IRI as well as human/murine *in vitro* cell models of hypoxia/reoxygenation suggest—though not generally confirmed so far—that oxidative stress may represent one of the types of stress able to upregulate various NKG2D-binding class III DAMPs

(9,158–160,208,276,277). In addition, in a clinical study on biopsies of renal allografts, expression of MICB molecules was shown before and after transplantation (278).

Class IV DAMPs

Class IV DAMPs refer to oxidative injury-induced neo-antigens/neo-epitopes (=oxidation-specific neo-epitopes) exposed on cells of postischemically reperfused tissue. As shown in studies of various IRI models (intestinal, skeletal muscle, and heart IRI models), these neo-epitopes bind to pre-existing autoreactive natural IgM antibodies (in terms of innate humoral PRRs) followed by activation of the mannose binding lectin–mediated complement cascade. As so far detected, these oxidation-specific neo-epitopes include nonmuscle myosin heavy chain IIA (NMHC-II), actin cytoskeleton, and phosphocholine of oxidized phospholipids and malondialdehyde (171,279–284).

This form of oxidative injury–induced activation of complement may contribute to generation of immunogenic DCs mainly through three pathways: via (i) the terminal products, 5b-9, known as the membrane attack complex, which may aggravate ROS-mediated cell and tissue injury (285), thereby inducting class I, class II, and class III DAMPs; (ii) the small fragments C3a and C5a, which may contribute to the creation of DC maturation-promoting inflammation (286–288); and (iii) C3a and C5a, which have been shown to directly activate human immature DCs associated with acquisition of phenotypic change and functional modulation (289).

Class V DAMPs

Finally, class V DAMPs refer to homeostatic danger signals (10), defining an altered pattern of molecules in terms of dyshomeostasis-associated molecular patterns. This class of DAMPs reflects microenvironmental perturbations in the steady state of a cell including but not limited to hypoxia, acidosis, redox imbalance, and changes in normal ion concentration as well as accumulation of unfolded/misfolded proteins as observed in ER stress.

Class V DAMPs, for example, reflected by intracellular stress-signaling ion perturbations sensed by NLRP3 and/or reflected by ER stress perceived by UPR sensors such as the protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK), may contribute to the generation of immunostimulatory DCs. For example, class V DAMPs emitted by ER stress (almost always associated with oxidative stress) under involvement of the UPR sensors were reported to contribute to DC maturation (290–293).

Adaptive Stress Responses: The First Wave of DAMP Emission

Under stressful and injurious conditions, cells in living tissue may survive or die via ACD and/or RCD. ACD is caused by extreme insults, including physical, thermal, chemical, and mechanical injurious stimuli; this kind of cell death is completely uncontrolled and virtually immediate (294). Cells exposed to such extreme and severe insults resulting in a catastrophic ACD passively release large amounts of DAMPs of nuclear, mitochondrial, and cytosolic origin due to an immediate and irreversible loss of the plasma membrane integrity. However, if an initial insult does not lead to an immediate ACD, the stressed/injured cell, during the dying process, actively generates various classes of DAMPs that induce adaptive stress responses by using genetically encoded molecular machineries. Such stress responses include the heat shock response (HSR), the UPR, and the DDR. When successful, these stress responses interact with each other to restore the cellular homeostasis and, thus, maintain cell survival. However, when unsuccessful, they result in a controlled destruction of the stressed cell, denoted as a RCD, a subtype of cell death that includes several cell-death modalities (Figure 3). Notably, RCD does not only occur as a consequence of molecular perturbations and cellular damage but also in the context of physiologic instances of RCD, generally referred to as "programmed cell death" (294).

The Heat Shock Response

The HSR—one of the most ancient and evolutionarily conserved cytoprotective mechanisms found in nature—is induced upon exposure of living cells to acute, subacute, or chronic stress conditions. This defense response is characterized by the expression of a group of phylogenetically conserved intracellular HSPs, which form a chaperone network involved in correct protein folding, trafficking, and complex assembly. HSPs mediate protective cellular defense mechanisms including regulation of apoptosis, the aim being to maintain and restore cellular protein homeostasis (proteostasis) (13,16,295–300). The molecules are induced by various environmental insults that can cause protein denaturation and unfolding within the cells, leading to formation of nonnative proteins and protein aggregates, thereby emitting class V DAMPs. Of note, besides their protective role in different intracellular compartments, HSPs can translocate to the cell surface to get exposed or are actively secreted via noncanonical pathways or passively released into the extracellular space as observed, for example, during an apoptotic process. Once emitted as operating class I DAMPs, HSPs are sensed by classical recognition receptors (e.g. TLR2/4) and/or nonclassical receptors (e.g. CD 91) (301–307). Of note, the processes of both IRI to allografts (9,15,16) and therapy-mediated injury to tumors (134–139,210) are associated with emission of HSPs.

In all eukaryotes, the HSR is primarily regulated and controlled by heat shock transcription factors (HSFs), in particular, HSF-1 that binds to heat shock elements in

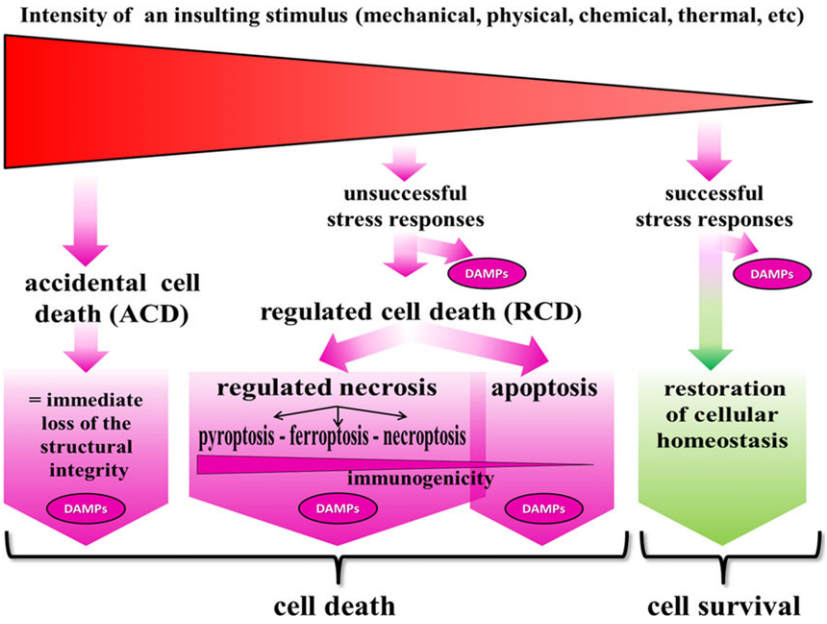


Figure 3: Schematic illustration of various sources of DAMPs. DAMPs are generated and emitted during stress responses and different forms of regulated cell death (associated with increasing degree of immunogenicity) in relation to the intensity of insulting stimuli. ACD, accidental cell death; DAMPs, damage-associated molecular patterns; RCD, regulated cell death. Note: On the level of "ferroptosis," other forms of regulated necrosis such as mitochondrial permeability transition-regulated necrosis (MPT-RN) and parthanatos possess similar immunogenic properties.

the promoters of target genes (308). For example, HSF1 is activated by oxidative stress and tumor-associated stress (309,310). In addition, HSF1 has been shown to regulate the expression of a class III DAMP, namely, MICB. Interestingly, downregulation of MICB by HSF1 knockdown resulted in a partial reduction in lysis of tumor cells mediated by NKG2D-expressing NK cells (311).

There is at least preliminary evidence suggesting that intracellular perturbations reflecting class V DAMPs may activate HSFs (312–315). Such molecular alterations reportedly include changes in cytosolic Ca^{2+} concentration, for example, caused by increase of fluidity in specific membrane domains (312,313). Interestingly, a recent study in support of these earlier findings provided evidence of the existence of a plasma membrane–dependent mechanism of HSF-1 activation in animal cells, which is initiated by specific membrane-dependent transient receptor potential vanilloid (TRPV) calcium channel–like receptors (314). These findings lend support to the assumption that heat-sensing and signaling in mammalian cells is dependent on TRPV channels, suggesting that these receptors may act as a major HSR sensor in different epithelial noncancerous and cancerous cells, capable of triggering the cellular HSR (314). In another line of experiments, TRPV2 was demonstrated to mediate the effects of transient heat shock on endocytosis of human monocyte–derived DCs, suggesting a central role of TRPV2 in mediating the cellular action of heat shock on these cells (315).

ER Stress and the UPR

The ER is a subcellular organelle in the control of proteostasis, responsible for calcium storage and lipid biosynthesis as well as the synthesis, correct folding, processing, maturation, and trafficking of proteins via the Golgi apparatus destined to be secreted or inserted into the plasma membrane. A series of chaperones, folding enzymes, glucosidases, and carbohydrate transferases support these processes. Perturbation of the ER-associated functions such as accumulation of unfolded/misfolded proteins, excessive ROS production, hypoxia, or viral infection reflects stress of the organelle and results in activation of an ER stress-coping response, the evolutionary conserved UPR (316–319). Of note, the processes of both IRI-mediated cell damage/cell death (80–82) and induction of "immunogenic cell death" (ICD) of cancer cells (320–322) (note: details of ICD will be outlined in [31]) are characterized by demonstration of ER stress that is almost always associated with oxidative stress and vice versa (323). To cope with ER stress, cells activate the UPR, a dynamic signaling network that orchestrates the recovery of homeostasis or triggers RCD modalities, depending on the level of damage. Perception of any perturbation of the ER is provided by three sensor molecules of the UPR: PERK,

inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6). The UPR-mediated recovery of ER homeostasis mainly occurs through the PERK-eukaryotic translation initiation factor 2α–mediated temporary shutdown of protein translation and the activation of a complex genetic program that aims to improve ER quality control and adaptive responses (316–319) (Figure 4). Accordingly, PERK, devoted to perceive class V DAMP-emitting ER perturbations (so far, there is no clear evidence for IRE1 and ATF6 in this respect), may be regarded as a new family of nonclassical PRRs, at least in a wider sense.

In nonstressed conditions, the three sensors of the ER homeostasis are kept in an inactive state by the ER luminal protein BiP/GRP78. However, in conditions of ER stress, BiP is titrated away from these sensors, allowing their activation to emanate pathways, collectively included in the term of UPR.

Under remediable ER stress conditions, the three sensors trigger signaling pathways to resolve ER stress, aiming at maintaining cellular integrity. For example, misfolded proteins are dislocated in the cytosol, where degradation processes such as the ER-associated degradation and autophagy will clear them, thereby reducing their potential toxicity (Figure 4). This process includes transcriptional activation of a variety of ER-associated chaperones and folding enzymes (324–328), which include—but are not limited to—BiP and the luminal CALR (290,318,329–331).

Typically, HSPs and CALR, like other chaperones, can translocate to the surface of cells through the ER-to-Golgi transfer and secretory pathway (210). Once exposed or released into the extracellular space, these molecules operate as class Ia/b DAMPs as mostly described in the context of induction of ICD (for details,

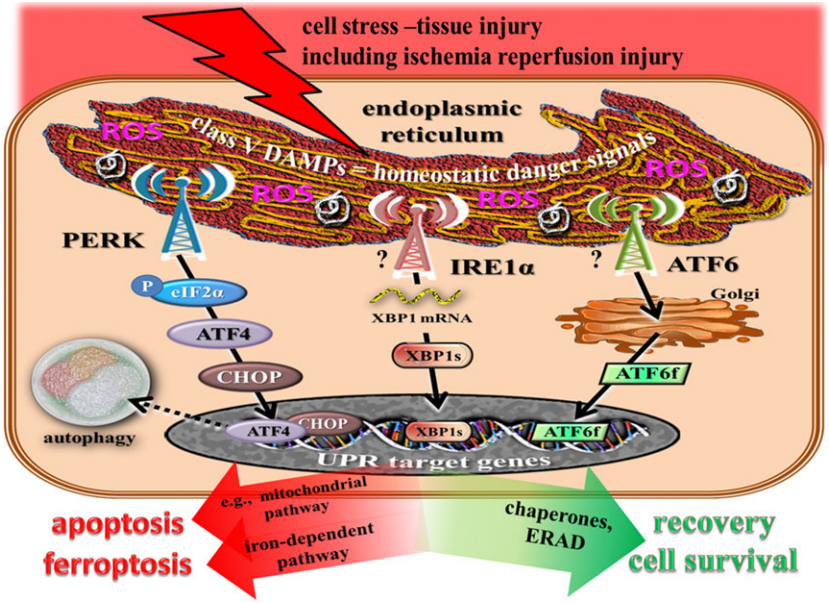


Figure 4: Simplified scenario model illustrating the ER stress-induced three arms of the unfolded protein response. All three ER stress sensors (PERK, IRE1α, and ATF6) are present in the ER membrane. PERK, devoted to perceive class V DAMP-emitting ER perturbations (so far, there is no clear evidence for IRE1 and ATF6 in this respect), may be regarded as a new family of nonclassical PRRs, at least in a wider sense. The three stress sensors activate signaling events to re-establish homeostasis in the ER and promote adaptation and cell survival. PERK phosphorylates eIF2α, which in turn increases the expression of the transcription factor ATF4. In the presence of low-grade ER stress, ATF4 induces the expression of *C/EBP homologous protein* (CHOP), which at low concentrations favors the induction of several genes central in cell survival and the UPR. If ER stress is prolonged, PERK greatly increases CHOP, thus favoring cell death. IRE1α signals through its RNase via the splicing of XBP1 mRNA. Active XBP1 enters the nucleus and increases the transcription of chaperones and other UPR-related proteins that enhance the ER-associated degradation (ERAD) of misfolded proteins. Finally, following ER stress, ATF6 is exported from the ER to the Golgi complex, where it is cleaved by the proteases S1P and S2P, releasing its cytosolic domain, which is a potent transcription factor. Together, UPR transcription factors determine cell fate by the regulation of distinct subsets of target genes toward recovery of ER homeostasis or the induction of apoptosis and ferroptosis. Under irremediable ER stress, the UPR actively promotes proteotoxicity, inflammatory responses, apoptosis, and ferroptosis, respectively. ATF, activating transcription factor; CHOP, cytidine-cytidine-adenosine-adenosine thymidine-enhancer-binding homologous protein; DAMPs, damage-associated molecular patterns; eIF2α, eukaryotic translational initiation factor 2α; ER, endoplasmic reticulum; ERAD, endoplasmic reticulum–associated degradation; IRE1α, inositol-requiring transmembrane kinase/endoribonuclease 1α; PERK, protein kinase-like eukaryotic initiation factor 2α kinase; PRRs, pattern recognition receptors; ROS, reactive oxygen species; UPR, unfolded protein response; XBP1, X-box binding protein 1.

see [31]) (117,321,332–335). Via this mechanism and by crosstalk with other molecular machineries of the innate immune system including the NLRP3 inflammasome activation via TXNIP, the UPR may contribute to sterile inflammation and immunity (240,241,244,324–327,336). In addition, several signaling cascades triggered by the three sensors are apparently potent inducers of autophagy at a cellwide level, a self-degradative catabolic process that normally has an adaptive/protective function and consists of three major types: chaperone-mediated, macro- and microautophagy. Interestingly, recent evidence has indicated that UPR-induced autophagic processes (337) are able to alleviate the UPR, pointing to a crosstalk between these two innate immune defense mechanisms (91,92). Remarkably, a complex relationship reportedly exists between autophagy and DAMPs in cellular adaption to stress and injury and cell death characterized by a crosstalk between autophagy induction and secretion or release of DAMPs. In fact, growing evidence indicates that autophagic mechanisms are involved in regulating release and degradation of DAMPs including CALR, HMGB1, ATP, and DNA in several cell types (118,321,338). This scenario may contribute to the observation that autophagy is also able to shape a supportive cellular immune response (339,340). This kind of innate immune interrelationship, outlined superficially here and further discussed in (31), is involved in both mechanisms of reperfusion-mediated cell injury and certain contexts of ICD modulation (72,73,91,94,341–347). On the other hand, autophagy can also play a role in the suppression of danger signaling; for example, ROS-induced autophagy downstream of ER stress during ICD can suppress surface exposure of CALR, thereby affecting various innate and adaptive immune effector mechanisms (118). Interestingly, a compensatory process of autophagy (i.e. chaperone-mediated autophagy) may have a role in facilitating surface exposure of CALR, functional consequences of which remain unverified (348).

In cases of severe irremediable ER stress, however, the balance is tipped in favor of pro-death signaling; that is, the UPR, now mediated by different biochemical pathways, may lead to pro-inflammatory and pro-apoptotic responses resulting in catastrophic RCD (Figure 4). In this context, it is interesting that one pathway of regulated necrosis (ferroptosis, see for details: RCD: An Efficient Source of DAMP Emission) clearly shares a partially overlapping machinery with ER stress, suggesting a molecular interconnectivity between these two events (349).

The DNA Damage Response

Maintaining genome integrity and transmission of intact genomes is critical for cellular, organismal, and species survival (350). This homeostatic integrity is threatened by DNA damage that occurs in a variety of conditions including but not limited to radiation, chemicals, and viral infections, two of the most dominant conditions being oxidative stress and replication stress (351–360).

In response to DNA damage, cells activate a complex network of cellular signaling pathways that cooperate to sense and repair lesions in DNA, denoted as the DDR. This stress response plays an important role against detrimental effects of cell stress and injury. It orchestrates many processes, including not only DNA repair but also regulation of cell cycle checkpoints, transcription of DDR genes, and autophagy (Figure 5). The DDR is instigated by the *ataxia telangiectasia mutated* and the *ataxia telangiectasia and Rad3-related* kinases (mostly nuclear proteins) that govern this complex network of effector pathways promoting DNA repair, cell cycle arrest, or apoptosis (361–366). Other lines of study lend support to the suggestion that DNA damage or DNA replication stress promotes release of aberrant DNA structures into the cytosol in the form of single-stranded (ss) and double-stranded (ds) DNA breaks that operate as class I DAMPs. They are sensed by the DNA receptor *cyclic GMP-AMP synthase* and probably other as-yet unidentified DNA receptors to activate *stimulator of interferon genes* (STING)–dependent pathways to promote defense pathways (367,368).

Of note, as shown in studies on tumor models, DDR reportedly induces the expression of numerous class III DAMPs including MICs and different ULBPs through the activation of STING-mediated pathways (161,368–371). Strikingly, the data suggest that DNA damage in lymphoma cells leads to the presence of class I DAMPs in form of cytosolic single-stranded DNA and dsDNA. As discussed by the authors (368), it is conceivable that cytosolic DNA is released by dysfunctional mitochondria upon DNA damage or generated during repair of damaged genomic DNA. However, when unsuccessful in repairing DNA damage, the DDR—like an UPR in case of irremediable ER stress—ultimately induces a RCD, most often in form of apoptosis (Figure 5) (363,364).

RCD: An Efficient Source of DAMP Emission

When—as briefly described here—adaptive stress responses such as the UPR and the DDR fail to repair molecular damage and, thus, fail to restore cellular homeostasis, cells generally promote and undergo RCD as a means to preserve the homeostasis of the whole organism. RCD represents an umbrella term that includes several subroutines of cell death, some of which are immunogenic and some, such as apoptosis, are not. By definition, regulated necrosis (RN) is immunogenic because of the inevitable rupture of the plasma membrane and consequent DAMP release, a process that does not happen during apoptosis because the plasma membrane integrity remains preserved in the latter. However,

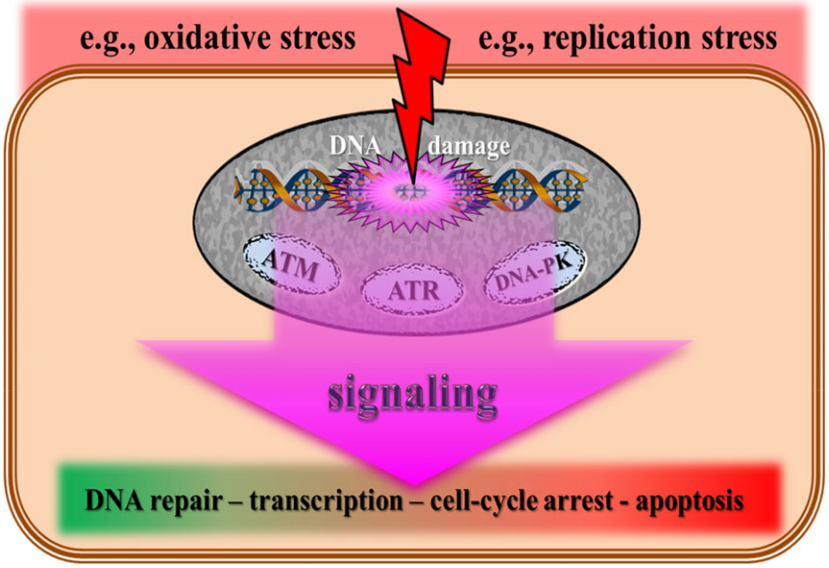


Figure 5: Simplified scenario model of the DNA damage response. DNA damage is caused by a variety of sources including oxidative stress and replication stress. The key regulators of the checkpoint pathways in the DNA damage response are the ATM and ATR protein kinases. These proteins are central to the entire DNA damage response. The cellular response to damage may involve activation of a cell cycle checkpoint, commencement of transcriptional programs, execution of DNA repair, or when the damage is severe, initiation of apoptosis. Upon sensing DNA damage, cell cycle checkpoints are activated to arrest cell cycle progression to allow time for repair before the damage is passed on to the cells. ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia, and Rad3-related; DNA-PK, DNA protein kinase.

several different pathways of RN have been recently described. But why are there so many different pathways of RN preserved? Currently, the most likely hypothesis appears to us to be the difference in immunogenicity (compare Figure 3).

As such, necroptosis, a kinase-mediated cell death that relies on *receptor-interacting protein kinase 3* (RIPK3) (372–374)–mediated phosphorylation of the pseudokinase *mixed-lineage kinase domain-like protein* (375,376), is associated with the generation of IL-33, a cytokine that appears to limit the proinflammatory signal to a limited focal area. In contrast, during GSDMD-mediated pyroptosis (377,378)—a process that is elicited by bacteria predominantly in macrophages—long-lasting cytokines such as IL-1β and IL-18 are matured in a caspase-dependent fashion. This results in a broader immune response without limitation to the primarily injured organ. Besides necroptosis and pyroptosis, several other RN pathways have not yet been associated with the production of cytokines or chemokines, rendering them just as immunogenic as they are by DAMP release. These RN subroutines include parthanatos, ferroptosis, and mitochondrial permeability transition–dependent regulated necrosis. RN in neutrophils is especially immunogenic because it appears to often be associated with the release of (neutrophil) extracellular traps (NETs), long DNA stretches that are released from the nuclei of neutrophils in a highly dynamic, highly immunogenic fashion. Death associated with this process is referred to as NETosis, and it was recently also demonstrated that this process depends on RIPK3, just like necroptosis (379). The best-studied variants of RCD, apoptosis and necroptosis, are briefly described here. The special instance of RCD, the ICD (294,380) will be outlined in the accompanying Review (31).

Apoptosis is a caspase-dependent variant of RCD (294). Dying cells have been defined as apoptotic by distinguishing features, including cell contraction, DNA cleavage, nuclear fragmentation, plasma membrane blebbing, exposure of phosphatidylserine, apoptotic body formation, and maintenance of intact cellular membranes to prevent massive protein release and consequent inflammation. It is only the latter that distinguishes apoptosis from RN pathways. Other than the kinase-mediated necroptosis pathway, apoptosis depends on proteases. In particular, this form of cell death involves the engagement of pathways that lead to the activation of members of the caspase family of cysteine proteases, which, in an orchestrated way, ultimately cause the morphologic features of this type of cell death. Apoptosis can be instigated by an intrinsic pathway that is initiated inside cells by mitochondrial release of pro-apoptotic factors or an extrinsic pathway that is initiated at the cell surface by death receptors that are members of the tumor necrosis factor receptor gene family (294,381–383). Of note, in the context of certain chemotherapeutics, oncolytic viruses, photodynamic therapy, and radiotherapy, cancer

cells undergoing apoptosis are rendered immunogenic, a cornerstone concept for ICD (210).

The detection of necroptosis changed our view on immunogenicity because it was for the first time that we could now imagine necrosis to be a regulated process that we can potentially interfere with. The biochemical processes in necroptosis are distinct from those found in apoptosis; in particular, there is no caspase activation. Necroptosis is induced by various insults and stimuli including death receptors, TLRs, NLRs, interferon receptor, intracellular RNA and DNA sensors (DAI), and probably other mediators (21,74,384–386). RIPK1 constitutively prevents the activation of RIPK3 by means of its *receptor-interacting protein homotypic interacting motif* (RHIM)-domain that directly engages the RIPK3 RHIM domain to prevent the autoactivation of RIPK3. It therefore contains important kinase-dependent and scaffolding functions that inhibit or trigger necroptosis. RIPK1 is involved in the regulation of apoptosis, mechanistically defining this molecule (and its posttranslational modification by polyubiquitination and phosphorylation) as the molecular switch between apoptosis and necroptosis, or immunogenic and nonimmunogenic cell death. Therefore, pharmacologic control of RIPK1 function has attracted massive attention by several pharmaceutical companies.

A current field of interest is the exploration of molecular relationships between apoptosis, necroptosis, and autophagy in regard to their roles in tumor growth, its counterpart allotolerance, or on the other hand tumor and allograft rejection (387–389). For example, preclinical studies have already revealed important functions for necroptosis in inflammation, suggesting that it could be implicated in the pathogenesis of many human inflammatory diseases, including IRI (390–392).

The recently recognized critical impact of RCD on instigation of immunity lies in the fact that this form of cell death leads to generation of significant amounts of DAMPs, though in graduated amounts compared to DAMP emission characteristic for an ACD. Though apoptosis was generally considered to be nonimmunogenic and believed not to generate DAMPs, recent studies demonstrated that, in fact, these molecules including HSPs, S100 proteins, and nucleosomal histones are released in limited amounts in the early apoptosis phase in defined experimental settings. This stage is characterized by blebbing and apoptotic body formation that is associated with limited membrane permeabilization allowing acute and localized release of immunomodulatory proteins (393).

By contrast, there is a general consensus that necroptosis associated with rapid plasma membrane permeabilization leads to a massive release of DAMPs from the disintegrating cell, albeit with parallel production of IL-33 (394), presumably to limit the function of the DAMPs to a defined area. In this sense, it is worth mentioning that

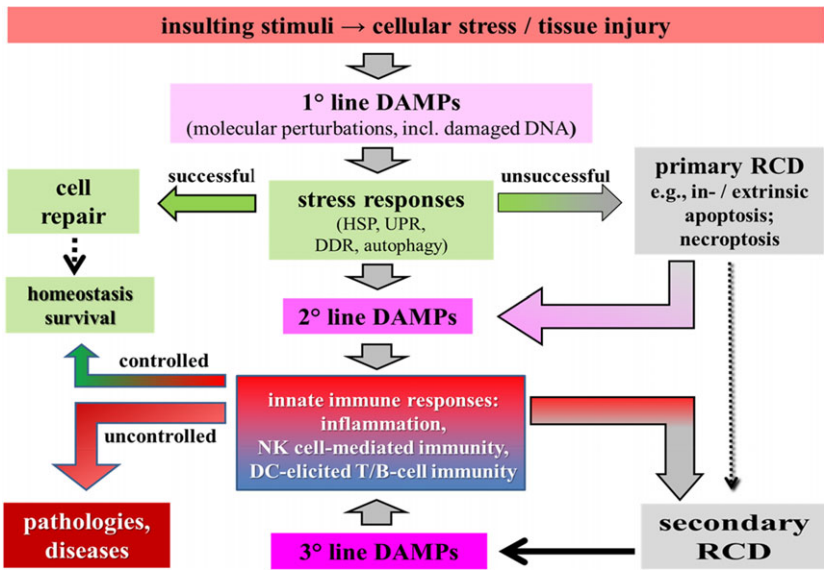


Figure 6: Schematic illustration: Stress responses and stress response-induced regulated cell death associated with the consecutive emission of three lines of DAMPs. The resulting promotion of innate and adaptive immune responses, when controlled, leads to homeostasis and survival, and when uncontrolled, exaggerated and overshooting, to pathologies and diseases. DAMPs, damage-associated molecular patterns; DC, dendritic cell; DDR, DNA damage response; HSP, heat shock protein; NK, natural killer; RCD, regulated cell death; UPR, unfolded protein response.

IL-33 stabilizes regulatory T cells via stimulation of the ST2 receptor (395). Moreover, necroptotic cells continue to synthesize proteins until the last moment before plasma membrane permeabilization (396,397), but the precise function of this feature remains unclear.

Similarly, in pyroptosis, no active release mechanism has been so far described that might result in the release of IL-1β and IL-18 in the absence of plasma membrane rupture. Given the difference in immunogenicity of RCD pathways, it is obvious that we shall focus on understanding the precise pathway of RCD that is involved, and the relative contribution of each of these pathways to organ damage and immunogenicity. This concept with respect to the RN pathways has also been referred to as necroinflammation (398,399).

Conclusions

In summary, any stressful or injurious stimulus to a cell can lead to either primary ACD or stress responses which, when unsuccessful, secondarily result in RCD. A growing amount of evidence suggests that these stress responses are triggered by a first line of injury-induced DAMPs such as "homeostatic" class V DAMPs in UPR or class I DAMPs in terms of DNA fragments in DDR.

Stress responses including concomitant autophagic processes, when successful, generate a second line of DAMPs that—also in terms of crosstalk with other molecular machineries of the defense system such as autophagy and inflammasomes—may contribute to induction of innate immune inflammatory and adaptive immune responses. For example, as also reviewed elsewhere (400), the UPR can promote and regulate adaptive immune responses and, likewise, the DDR may alert the immune system to DNA damage through emission of class III DAMPs to activate immune receptors such as NKG2D on NK cells, NK T cells, and γδ T cells.

Intriguingly, when unsuccessful, these adaptive responses also lead to emission of large amounts of second-line ("apoptotic/necroptotic") DAMPs, this time associated with the induction of a primary RCD. These DAMPs, via PRR-mediated innate immune pathways, may lead again to inflammatory and adaptive immune responses that, when controlled, may contribute to homeostasis and survival, but when uncontrolled, may promote pathologies and diseases. In addition, the inflammatory response may drive a secondary RCD, eventually promoting a third line of DAMPs, a phenomenon called "propagation of RCD" (390,396) (Figure 6).

Finally, it seems worthwhile to explore whether or not first-line DAMPs together and in relation with subsequent emission of second-line DAMPs—eventually in terms of a "hierarchical principle" in their mutual communication—form a distinct DAMP signature that represents a *conditio sine qua non* needed to promote an adaptive immune response. Such an endeavor appears to be of high interest in view of the scenario of DAMP emission as a consequence of adaptive stress responses and RCD that is associated with both reperfusion-mediated (allogeneic) cell injury and ICD of cancer cells.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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