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REVIEW

The Role of Damage-Associated Molecular Patterns in Human Diseases

Part I - Promoting inflammation and immunity

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دور أنماط الضرر الجزيئية المرتبطة في الأمراض البشرية

الجزء الأول

تعزيز الالتهاب والمناعة

والتر ج لاند

ABSTRACT: There is increasing interest by physicians in the impact of the innate immune system on human diseases. In particular, the role of the molecules that initiate and amplify innate immune pathways, namely damage-associated molecular patterns (DAMPs), is of interest as these molecules are involved in the pathogenesis of many human disorders. The first part of this review identifies five classes of cell stress/tissue injury-induced DAMPs that are sensed by various recognition receptor-bearing cells of the innate immune system, thereby mounting inflammation, promoting *apoptosis* and shaping adaptive immune responses. The DAMPs activate and orchestrate several innate immune machineries, including inflammasomes and the unfolded protein response that synergistically operates to induce inflammatory, metabolic and adaptive immune pathologies. Two examples of autoimmune diseases are discussed as they represent a typical paradigm of the intimate interplay between innate and adaptive immune responses.

Keywords: Soft Tissue Injury; Innate Immunity; Inflammation; Receptors, Pattern Recognition; Autoimmunity.

الملخص: هناك اهتمام متزايد من قبل الأطباء في أثر نظام المناعة الفطري على مرض الإنسان. و تلعب الجزيئات المضخمة لمسارات المناعة الفطرية، وبخاصة أنماط الضرر الجزيئية المترابطة (DAMPs)، دورا مهما في التسبب في العديد من الاضطرابات للإنسان.
يحدد الجزء الأول من هذا الاستعراض خمس فئات من صور إجهاد الخلايا/إصابات الأنسجة الناجم عن DAMPs، التي يشعر بها الجسم بواسطة الخلايا الحاملة للمستقبلات التابعة لنظام المناعة الفطري، والتي تؤدي إلى تصاعد الالتهاب، وتعزيز موت الخلايا المبرمج وتشكيل الاستجابات المناعية التكيفية. تفعل ال DAMPs عدة آليات للمناعة الفطرية بصورة منسجمة، بما في ذلك الأجسام الالتهابية واستجابة البروتين المفتوحة التي تعمل بالتآزر لإحداث الأمراض المناعية الالتهابية التكيفية. ونناقش مثالين من أمراض المناعة الذاتية حيث إنها تمثل نموذجا للتفاعل الحميم بين الاستجابات المناعية الفطرية والتكيفية.

مفتاح الكلمات: إصابات الأنسجة الرخوة؛ المناعة الفطرية؛ التهاب؛ المستقبلات، التعرف على الأنماط؛ المناعة الذاتية.

Over 20 years ago, the danger/injury model was formulated, claiming that cell stress/tissue injury induces immunity rather than the presence of that which is 'non-self'. The model emerged from two sources. First, its original discovery was based on a clinical trial in transplant patients which provided compelling evidence that tissue injury (allograft injury) induces immunity in the form of alloimmunity-mediated allograft rejection.[1] Second, Matzinger described a self-coherent argument on theoretical grounds which concluded stringently that the self/non-self discrimination theory of immune responses was inappropriate.[2] After the (re)discovery of innate immunity, the danger/injury theory was modified by both groups several times.[3–8] It has now been proposed that endogenous molecules released from stressed or dying cells—termed damage- or danger-associated molecular patterns (DAMPs), in analogy to the term pathogen-associated molecular patterns (PAMPs)—are recognised by pattern recognition receptors (PRRs) expressed on/in innate immune system cells to promote inflammatory pathways. Further, it was stressed that the sensing of DAMPs by PRR-bearing dendritic cells (DCs) promotes their maturation/activation which is associated with the acquisition of immunostimulatory capacities to elicit an adaptive immune response.[3–8] Land reported that DAMPs, "such as heat shock proteins (HSPs), arising in the stressed allograft, serve as endogenous ligands for and interact with Toll-

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like receptors (TLRs) on cells of the innate immune system such as donor- or recipient-derived DCs and donor-derived vascular cells and, by this engagement, activate them".[7]

Today, DAMPs have gained worldwide acceptance and these molecules are involved in the pathogenesis of many human diseases. In fact, the modern interpretation of the danger/injury model suggests that most human disorders stem from disturbed/perturbed physiological homeostasis as reflected by tissue injury, cell stress or even a slight metabolic disruption of the extra/intracellular microenvironment. Human diseases are now seen to unfold in light of injury-induced innate immune events. The principal sequelae of pathological events are: microbial/non-microbial (sterile) stressful stimuli/inciting insults > cell stress/tissue injury > elicitation of DAMPs > recognition by PRR-bearing innate immune cells > activation of the innate immune system > infective/sterile inflammatory response. Eventually, in the presence of microbial, altered-self antigens or tumour antigens, there is an adaptive immune response.

However, it is important to emphasise that a complete overview of all clinical disease entities or murine disease models is not provided here. Rather, the intent of this review is to highlight a few clinical diseases considered to be prototypical of the above-mentioned aetiopathogenic sequelae. With this in mind, this review is divided into two. Part I serves as a brief introduction to the function of DAMPs in autoimmune diseases, particularly systemic *lupus* erythematosus (SLE) and rheumatoid arthritis (RA). Part II, to be published at a later date, will investigate their relationship with atherosclerosis, metabolic and neurodegenerative disorders, cancer and infection. In this article, a few relevant aspects of DAMPs-induced innate immune mechanisms and responses will be described and discussion limited to those DAMPs that are currently known to play a major role in human diseases. More comprehensive reviews on the biology of DAMPs have been published previously.[9,10]

Damage-Associated Molecular Patterns Promote Inflammation and Adaptive Immunity

The innate immune system is a highly sensitive organ of perception; it consists not only of mobile immune cells responsible for evoking inflammatory and adaptive immune responses (e.g. neutrophils, macrophages and DCs), but also of somatic cells responsible for mounting fibrogenesis/fibrosis (including epithelial cells, fibroblasts and smooth muscle cells). All of these different cells are equipped with PRRs to sense cell stress and tissue injury. The major response to inciting insults is inflammation, with the aim of providing protection to the host.[11] This includes killing invading pathogens, removing damaged/dead cells, repairing destroyed tissue via wound healing, balancing metabolic or psychological irregularities and inducing a supportive adaptive immune response when foreign antigens (e.g. altered self-, tumour or microbial antigens) are involved. It is important to note that inflammatory responses to infection and sterile tissue injuries have different purposes. The former aims to protect the host from infection and can be coupled with the induction of adaptive immunity, whereas the latter primarily serves to promote tissue repair.[11]

However, although initially beneficial, innate immunity-mediated, protective inflammatory repair processes can become pathogenic. This may occur when there is a low-grade immune response which is not efficient enough to eliminate the inflammatory trigger, resulting in inappropriate insult resolution associated with chronic inflammation. Additionally, this can also occur when the response is exaggerated and uncontrolled—mostly associated with an overproduction of DAMPs—resulting in acute systemic hyperinflammatory disorders associated with 'collateral damage' or chronic overshooting repair processes accompanied by fibrosis. In both of these scenarios, DAMPs are significantly involved by representing the pathological trigger of subsequent pathogenetic pathways—but what is the nature of these molecules and how do they function?

FUNCTION AND CLASSES OF DAMAGE-ASSOCIATED MOLECULAR PATTERNS

DAMPs are intracellularly sequestered molecules that remain unrecognised by the immune system under normal physiological conditions. However, under conditions of cellular stress or tissue injury, these molecules are either actively secreted by stressed immune cells (e.g. exposed on stressed cells in terms of neo-antigens) or passively released into the extracellular environment from dying cells or the damaged extracellular matrix.[10,12–14] Of note, homeostatic danger signals have recently been reported as an emerging class of DAMPs;[12] here denoted as dyshomeostasis-associated molecular patterns, defining an altered pattern of molecules reflecting perturbations in the steady-state of the intra- and/or extracellular microenvironment which, for example, is observed in endoplasmic reticulum (ER) stress. In the literature, various definitions and interpretations of DAMPs can be found. Therefore,

Table 1: Classification of selected injury-induced damage-associated molecular patterns[7–10,12–14]

Class and description	Category of respective cell-bound/humoral pattern recognition receptors/sensors
I* DAMPs recognised by binding to a receptor, including HMGB1, HSPs, fHA and nucleic acids (e.g. mtDNA and cytosolic RNA).	TLRs, RAGE, RIG-I, MDA5, cGAS, IFI16, on macrophages, DCs and many somatic cells (e.g. fibroblasts).
II* DAMPs sensed without direct binding to a pattern recognition receptor, including eATP, MSU, TXNIP, ROS and others.	NLRP3 inflammasome, in macrophages, DCs and other somatic cells (e.g. islet cells).
III MICA, MICB and ULBPs.	Activating receptor NKG2D, expressed on innate lymphocytes (e.g. NK cells) and innate-like T lymphocytes (e.g. gamma delta T cells).
IV Neo-antigens such as NMHC-IIA, actin cytoskeleton, oxidised phospholipids and others.	Pre-existing natural IgM antibodies able to activate the complement cascade via the classical, MBL and alternative pathways.
V* Dyshomeostasis-associated molecular patterns, such as ER stress-inducing molecules (due to accumulating unfolded/misfolded proteins, changes in acidity and osmolarity, hypoxia, oxidised proteins, etc.).	Signalling sensors of the unfolded protein response (PERK, IRE1α → XBP1, ATF6).

DAMPs = damage-associated molecular patterns; TLRs = Toll-like receptors; RAGE = receptor for advanced glycation end-products; RIG-I = retinoic acid inducible gene-I; MDA5 = melanoma differentiation-associated gene 5; cGAS = cyclic guanosine monophosphate-adenosine monophosphate synthase; IFI16 = interferon gamma-inducible protein 16; HMGB1 = high-mobility group box 1; HSPs = heat shock proteins; DCs = dendritic cells; fHA = fragment of hyaluronan; mtDNA = mitochondrial DNA; RNA = ribonucleic acid; NLRP3 = nucleotide-binding oligomerisation domain-like receptor-containing pyrin domain 3; eATP = extracellular adenosine triphosphate; MSU = monosodium urate; TXNIP = thioredoxin-interacting protein; ROS = reactive oxygen species; MICA = major histocompatibility complex (MHC) class I chain-related protein A; MICB = MHC class I chain-related protein B; ULBPs = UL16 binding proteins; NKG2D = natural killer group 2 member D; NK = natural killer; IgM = immunoglobulin M; NMHC-IIA = non-muscle myosin heavy chain II-A; MBL = mannose-binding lectin; PERK = protein kinase-like eukaryotic initiation factor 2α kinase; IRE1α = inositol-requiring transmembrane kinase/endoribonuclease 1α; XBP1 = spliced X-box binding protein 1; ER = endoplasmic reticulum; ATF6 = activating transcription factor 6.

**Classifications designed for didactic purposes only as some DAMPs reportedly show overlapping functions.*

in the current article, DAMPs are didactically divided into five classes, with a particular focus on classes I, II and V [Table 1].

The various classes of sterile inflammation-promoting DAMPs, like infectious inflammation-evoking PAMPs, are sensed by a variety of distinct PRRs, promoting an inflammatory response. Many PRRs and their triggered signalling pathways have been comprehensively reviewed.[15–22] Figure 1 shows some selected DAMPs which are recognised by their cognate PRRs to trigger signalling pathways. TLR2 senses HSPs, hyaluronan and high-mobility group box 1 (HMGB1) with the subsequent myeloid differentiation primary response 88 (MyD88)-dependent pathway that turn on IκB kinase complex (IKKs) and mitogen-activated protein kinases (MAPKs), leading to the activation of nuclear factor *kappa* B (NF-κB) and activator protein-1 to induce inflammatory cytokines. TLR4 senses HSPs and HMGB1 with subsequent MyD88- and Toll/interleukin (IL)-1 receptor-domain-containing adapter-inducing interferon-β (TRIF)-dependent pathways that turn on IKKs, MAPKs and serine/threonine-protein kinase-binding kinase 1 (TBK1), leading to the activation of NF-κB and interferon regulatory factor 3 (IRF3) to induce type I interferons (IFNs) and cytokines. TLR3 senses double-stranded ribonucleic acid (RNA) with subsequent TRIF-dependent pathways that turn on TBK1, leading to the activation of IRF3 to induce type I IFNs. TLR7/8 (TLR8 only in humans), sensing single-stranded RNA, and TLR9, sensing DNA, use the adaptor molecule MyD88 for further signalling. In plasmacytoid DCs (pDCs), TLR7/8 and use the MyD88-dependent pathway leading to the activation of IRF5 and NF-κB to induce inflammatory cytokines and IRF7 to induce type I IFNs. Retinoic acid-inducible gene-I senses RNA with a subsequent mitochondrial antiviral signalling-dependent pathway that turns on IKKs and TBK1, leading to the activation of NF-κB and IRF3 to induce type I IFNs and cytokines. Cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) synthase (cGAS) and interferon gamma-inducible protein 16 sense DNA with the subsequent stimulator of interferon genes (STING)-dependent pathway that turns on TBK1, leading to the activation of IRF3 to induce type I IFNs [Figure 1].[15,16,19–21]

In particular, the recent discovery of the cGAS-cGAMP-STING pathway has led to the recognition that a loss of negative regulation of cytosolic DNA sensing will result in the aberrant recognition of self-DNA, which is strongly associated with the pathogenesis of autoimmune diseases such as *lupus*.[20] Wu *et al*. suggest that an increasing understanding of cytosolic nucleic acid sensing and of self/altered or self/non-self-discrimination mechanisms at the molecular level will help in clarifying the pathogenesis of autoimmune diseases.[20]

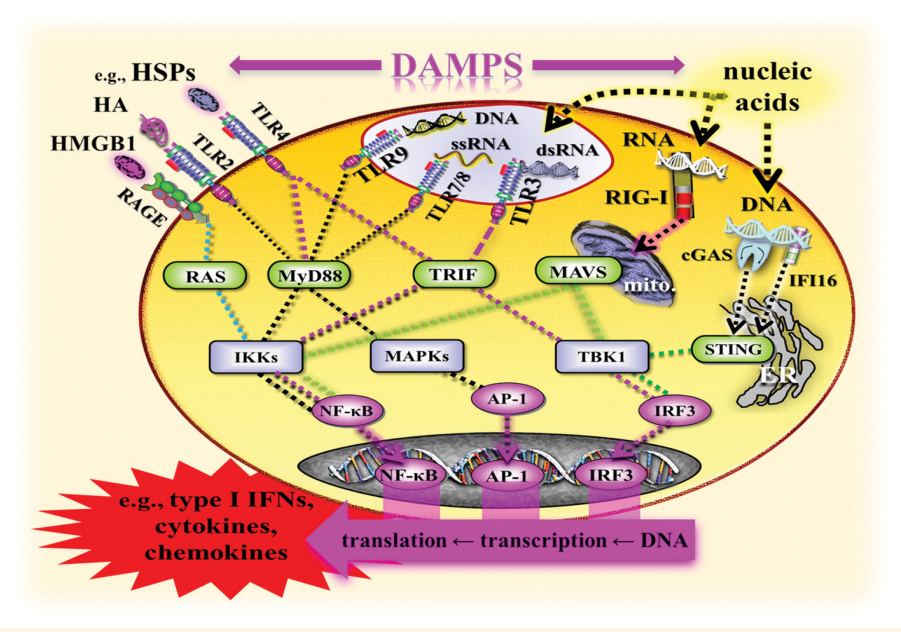

Figure 1: Simplified model illustrating DAMPs and their cognate PRRs triggering selected signalling pathways involved in mounting inflammatory responses. The PRRs are located in TLR2 and 4, RAGE (cell membrane-bound), TLR3, 7/8 and 9 (endosomal membrane-bound), cGAS, IFI16 and RIG-I (cytosolic).

DAMPs = damage-associated molecular patterns; PRRs = pattern recognition receptors; TLR = Toll-like receptor; RAGE = receptor for advanced glycation end-products; cGAS = cyclic guanosine monophosphate-adenosine monophosphate synthase; IFI16 = interferon gamma-inducible protein 16; RIG-I = retinoic acid inducible gene-I; HSPs = heat shock proteins; HA = hyaluronan; HMGB1 = high-mobility group box 1; ssRNA = single-stranded ribonucleic acid; dsRNA = double-stranded RNA; MyD88 = myeloid differentiation primary response 88; TRIF = Toll/interleukin-1 receptor-domain-containing adapter-inducing interferon-β; MAVS = mitochondrial antiviral signalling; RAS = ras protein; Mito = mitochondria; IKKs = IκB kinase complex; MAPKs = mitogen-activated protein kinases; TBK1 = serine/threonine-protein kinase-binding kinase 1; STING = stimulator of interferon genes; ER = endoplasmic reticulum; NF-κB = nuclear factor kappa B; AP-1 = activator protein-1; IRF3 = interferon regulatory factor 3; IFNs = interferons.

Green = adaptor molecules. Blue = distal kinases. Pink = transcription factors.

DAMAGE-ASSOCIATED MOLECULAR PATTERNS EVOKE INFLAMMATION AND APOPTOSIS

Innate immune cells constitute the first line of defence and are involved in recognising an initial threat, containing infectious/sterile insults and promoting the recruitment of additional immune cells through the release of cytokines and chemokines. Thus, inflammation serves as a tissue protective mechanism in mammals. On the other hand, *apoptosis* (a form of programmed cell death) can be regarded as a species-wide evolutionary-conserved cellular protective mechanism. Both protective mechanisms are promoted by DAMPs via inflammasome-independent and -dependent innate immune pathways. Of note, the IL-1 family of cytokines (IL-1α and -1β) plays a key role in infectious/sterile inflammatory diseases.[23–25] Both IL-1α and -1β provoke potent pro-inflammatory events by engaging the IL-1 receptor. Following tissue damage and necrosis, biologically active IL-1α can be released, serving as the primary initiating signal to coordinate mobilisation of immune cells to the damaged area.[23,24] IL-1α signalling results in dramatic production of cytokines and chemokines that function to orchestrate the expansion and recruitment of phagocytes to the site of damage. IL-1β also plays a crucial pathogenic role in multiple major inflammatory and autoimmune diseases.[23,24] However, while IL-1α is constitutively expressed in both immune and parenchymal cells, thus not requiring biological processing, IL-1β is not expressed at appreciable levels by circulating cells and therefore has to be processed.[23,24] The most well-characterised mechanism for processing IL-1β is via activated caspase-1 in the canonical inflammasome complex.

Canonical inflammasomes are multiprotein complexes that generally consist of three main components: a cytosolic sensor molecule, the enzyme caspase-1 and the adaptor protein *apoptosis*-associated speck-like protein containing caspase-recruit-ment domain (ASC). Members of the nucleotide-binding oligomerisation domain-like receptor (NLR) and AIM2-like receptor (ALR) families are established cytosolic sensor molecules that mediate inflammasome formation.[22,26–28] Certainly, DAMPS-activated inflammasomes play a pivotal role in promoting innate immune pathways to mount inflammation and shape adaptive immune responses. In particular, the NLR-containing pyrin domain 3 (NLRP3) inflammasome—the most studied

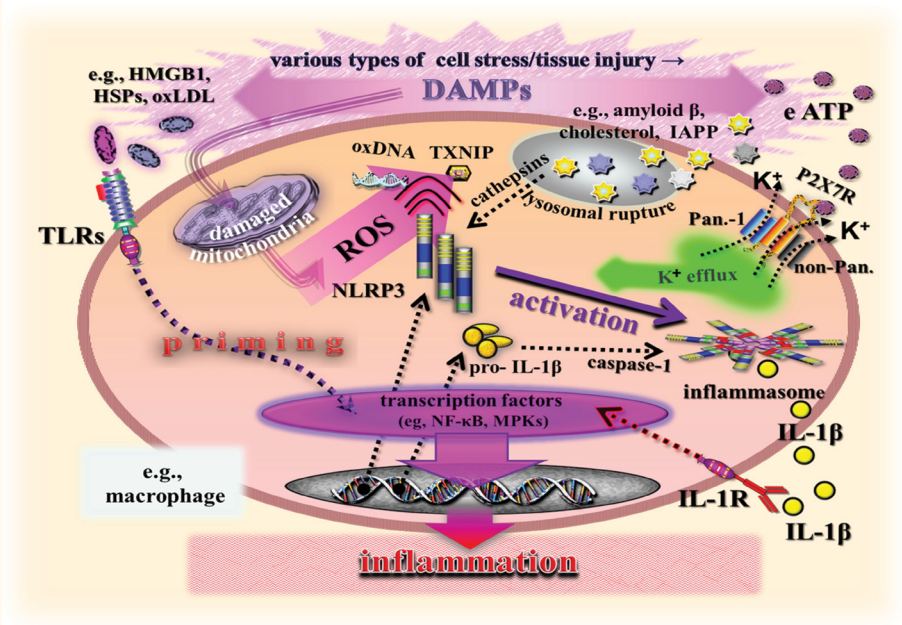

Figure 2: Simplified model illustrating the DAMPs-induced activation of the NLRP3 inflammasome.

DAMPs = damage-associated molecular patterns; NLRP3 = nucleotide-binding oligomerisation domain-like receptor-containing pyrin domain 3; HMGB1 = high-mobility group box 1; HSPs = heat shock proteins; oxLDL = oxidised low-density lipoproteins; eATP = extracellular adenosine triphosphate; IAPP = islet amyloid polypeptide; oxDNA = oxidised DNA; TXNIP = thioredoxin-interacting protein; P2X7R = P2X purinoceptor 7; K^+ = potassium ion; TLRs = Toll like receptors; ROS = reactive oxygen species; Pan.-1 = pannexin 1 haemichannel; non-Pan. = non-pannexin 1 haemichannel; IL-1β = interleukin-1 (IL-1)-beta; NF κB = nuclear factor kappa B; MPKs = mitogen activated protein kinases; IL-1R = IL-1 receptor.

inflammasome to date—operates as a key signalling platform contributing non-exclusively to DAMPs-induced sterile inflammatory/adaptive immune T cell responses. This occurs via the production of key cytokines IL-1β and -18, but may also instigate proapoptotic/pyroptotic pathways.[27,29] *Pyroptosis* is a rapid inflammatory form of cell death that shares characteristics with both *apoptosis* (such as DNA fragmentation) and necrosis (such as cell swelling and rupture).

Apart from extracellular pathogen-derived PAMPs, many DAMPs elicited by various types of cellular stress/tissue injury trigger activation of the NLRP3 inflammasome. In these instances, the activation status is modulated to avoid aberrant activation. In particular, there is evidence suggesting a two-step activation process: an initial priming step and a secondary activating step that activates the NLRP3 inflammasome assembly.[22,27–30] Thus, in macrophages, recruitment of NLRP3 and upregulation of pro-IL-1β/-18 protein levels are controlled by the transcriptional priming step triggered by class I DAMPs that stimulate PRRs such as TLRs upstream of the transcription factor NF-κB. Subsequently, class II DAMPs, including cholesterol, uric acid crystals and amyloid-β derived from lysosomal leakage and mediated via ion fluxes (potassium efflux and calcium [Ca] influx) activate the NLRP3 inflammasome assembly.

Therefore, priming (through class I DAMPs such as HMGB1, HSPs or oxidised low-density lipoproteins) via TLR sensing induces transcription-mediated and mitochondrial reactive oxygen species (ROS)-promoted upregulation of the NLRP3 receptor and production of pro-IL-1β. Finite activation of the inflammasome is provided by class II DAMPs (such as thioredoxin-interacting protein [TXNIP], extracellular adenosine triphosphate [eATP], cholesterol, islet amyloid polypeptide [IAPP] and amyloid β) which are directly or indirectly sensed by NLRP3 via various mechanisms. However, there is scarce evidence that NLRP3 binds directly to all of the different class II DAMPs. In fact, NLRP3 is believed to act as a sensor rather than a true receptor and its activation is thought to be triggered by signalling intermediates. Moreover, the events leading to NLRP3 activation appear to involve pathways mediating mitochondrial damage and the release of mitochondrial content into the cytosol, such as oxidised mitochondrial DNA. In addition, high levels of eATP activate NLRP3 after eATP binds to the P2X purinoceptor 7. Moreover, ROS production has a pivotal role in NLRP3 activation. In fact, ROS may exert its activating effect indirectly or directly by leading to the dissociation of TXNIP from thioredoxin, freeing the protein to interact with and activate NLRP3. Although the exact mechanisms are still unclear, activation of NLRP3 allows inflammasome complex formation and maturation of pro-IL-1β and

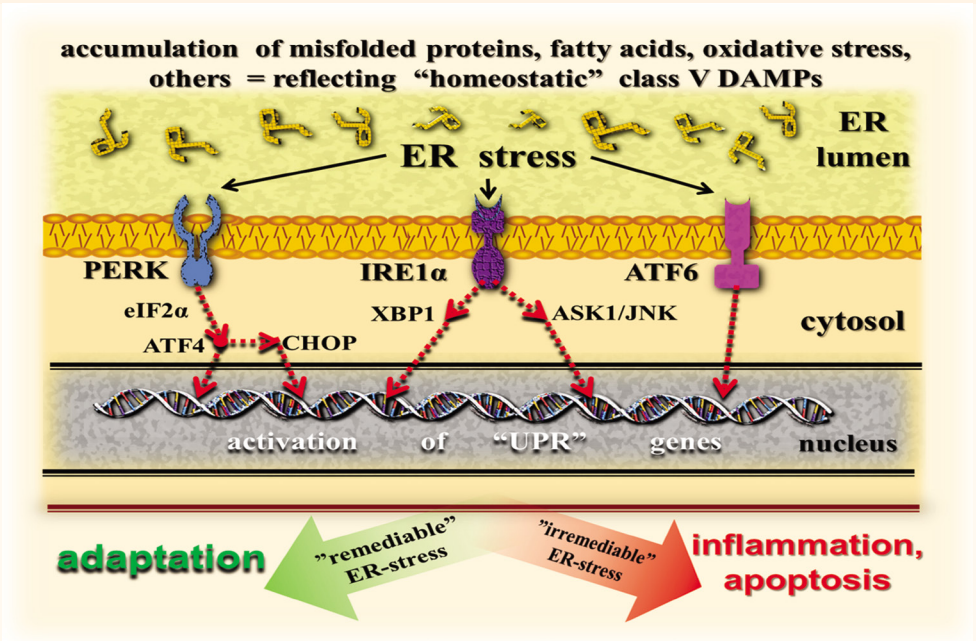

Figure 3: Simple model illustrating ER stress and the UPR.

ER = endoplasmic reticulum; UPR = unfolded protein response; DAMPs = damage-associated molecular patterns; PERK = protein kinase-like eukaryotic initiation factor 2α kinase; IRE1α = inositol-requiring transmembrane kinase/endoribonuclease 1α; ATF = activating transcription factor; eIF2α = eukaryotic translational initiation factor 2α; XBP1 = X-box binding protein 1; ASK1 = apoptosis-signalling kinase 1; JNK = c-JUN N-terminal kinase; CHOP = cytidine-cytidine-adenosine-adenosine-thymidine-enhancer-binding homologous protein.

18 via caspases 1 cleavage to secretion of bioactive IL-1β and -18 after caspase-1-dependent proteolysis from their pro-forms. These key cytokines, in an autocrine or paracrine manner, then lead to IL-1 receptor-triggered transcriptional pathways resulting in the production of further pro-inflammatory mediator substances (such as IL-6, chemokines and adhesion molecules) to create full scale tissue inflammation [Figure 2].[17,26–30]

Notably, besides the secretion of these two key cytokines, capase-1 activation has been shown to result in cell death via *pyroptosis*. Of note, although numerous potential unifying models for NLRP3 activation have been presented, no single mechanism proposed thus far appears to account for all possible pathways of how DAMPs activate NLRP3. In addition, it has become increasingly apparent that inflammasome activation is not as simple as once thought and additional caspases, including caspase-8 and -11, as well as other modulators, have been found to play critical roles in IL-1β cleavage and secretion.[25,27,29,30]

A new player has also recently entered the arena of innate immunity: the unfolded protein response (UPR).[31,32] Emerging evidence indicates that the UPR may play a significant role in human diseases as an essential tool of the innate immune system by allowing crosstalk with other molecular machineries of the defense system, such as the NLRP3 inflammasome. The UPR regulates any ER stress associated with, for example, the accumulation of unfolded/misfolded proteins.[33–36] The ER is a subcellular organelle of the eukaryotic cell that is responsible for Ca^{2+} ion 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. Perturbations of the ER reflect the generation of homeostatic danger signals (class V DAMPs) sensed by three UPR sensor molecules: the protein kinase-like eukaryotic initiation factor 2α kinase (PERK), inositol-requiring transmembrane kinase /endoribonuclease 1α (IRE1α) and activating transcription factor 6 (ATF6).

In non-stressed conditions, these 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 (e.g. the depletion of Ca^{2+} ions, increase in Ca^{2+} concentration, overloading of unfolded/misfolded proteins within the ER lumen, disturbances in lipid metabolism or changes in the ER redox state), BiP is titrated away from these sensors in order to carry out its chaperoning functions that are crucial for the correction of ER homeostasis. This allows the activation of the three sensors and their emanating signalling pathways, collectively termed as the UPR, strive to restore ER homeostasis. Under remediable ER stress conditions, the three sensors trigger signalling pathways to resolve ER stress; this is the pro-survival facet that is used to maintain cellular integrity (adaptive response). This facet includes processes like PERK-mediated phosphorylation of

eukaryotic initiation factor 2 (eIF2) that is required in the initiation of translation. This translation initiation factor functions by leading to temporary attenuation of the protein synthesis, which allows the load of incoming naïve proteins to be reduced. Further, eIF2 stimulates retention of Ca^{2+} and prevents aggregation of unfolded proteins by IRE1α and ATF6-mediated transcription of the X-box binding protein 1 (XBP1). XBP1 is a transcription factor that regulates the expression of genes important for the proper functioning of the UPR by ensuring the transcription of ER chaperones.[33–36]

However, in cases of severe irremediable ER stress, the balance is tipped in favor of pro-death signalling; that is, the UPR may lead to pro-inflammatory and proapoptotic responses, resulting in catastrophic cell death [Figure 3]. This part of the cascade is mediated by different processes, like PERK-mediated upregulation of the cytidine-cytidine-adenosine-adenosine-thymidine-enhancer-binding homologous protein (CHOP), which induces the downregulation of B-cell lymphoma 2 (Bcl-2) and the transcriptional activation of ER-oxidase 1α, finally leading to *apoptosis*. Additionally, IRE1α is also known to play a role in ER stress-induced *apoptosis*.[31,32,36,37]

In summary, the three sensor molecules (PERK, IRE1α and ATF6) serve as tools of the innate immune system to combat dangerous cell stress; thus, they operate as recognition receptors similar to TLRs or NLRs. In their function as sensors, these three molecules may be regarded as a new family of PRRs, at least in a wider sense, which are able to sense homeostatic danger signals in terms of class V DAMPs.

DAMAGE-ASSOCIATED MOLECULAR PATTERNS SHAPE ADAPTIVE IMMUNITY

The important role of DAMPs in human diseases is reflected by their capacity to initiate innate immune pathways that not only lead to tissue inflammation but also, via activation of specialised antigen-presenting cells (APCs), shape the adaptive immune responses involved in autoimmunity and anti-tumor and antimicrobial immunity. Doubtlessly, the key event of innate immunity that initiates and induces pathways, ultimately resulting in the development of an adaptive immune response, is seen in the DAMPs-induced maturation of steady-state immature DCs (iDCs) into immunostimulatory DCs. In short, the professional APCs translate innate immunity to adaptive immunity, dictating the type and course of adaptive immune responses. As reviewed elsewhere, this fundamental process of tissue injury-induced DC maturation involves large-scale changes in the expression of genes encoding a broad array of proteins.[10,12,37,38] These changes include, but are not limited to, the upregulation of expression of major histocompatibility complex (MHC) molecules (signal 1) and costimulatory molecules (signal 2), the secretion of type 1 T-helper (Th1) and Th17 polarising cytokines such as IL-12 (signal 3), and, lastly, the secretion of chemokines such as C-C chemokine receptor type 7 (CCR7) enabling maturing DCs to migrate to T cell areas within the secondary lymphoid organs.[10,12,37,38] Interestingly, during this process, DCs undergo a metabolic transition from oxidative phosphorylation to aerobic glycolysis. Having developed these characteristic properties, the cells then instruct naïve T lymphocytes in the host's secondary lymphoid tissue to mount adaptive immune responses.

All five classes of DAMPs, via different direct and indirect mechanisms, have been shown to promote the development of those immunostimulatory DCs that are able to efficiently present antigens (altered-self, tumour or microbial antigens), together with signal 2 and 3, to naïve T cells, thereby eliciting an adaptive immune response [Figure 4].[10,12,37,39] Thus, class I DAMPs (such as HMGB1 and HSP70) directly stimulate PRRs (such as TLRs of DCs) to initiate pathways leading to their activation. This may occur via recognition by TLR4 (essential for DC activation in an anti-tumour T cell response), TLR2 or the receptor for advanced glycation end-products (RAGE). Further, nucleic acids acting as class I DAMPs, such as double-stranded DNA (dsDNA), are recognised by TLR9 and other DNA sensors (such as cGAS as recently shown in murine conventional DCs). These are key events in converting iDCs to mature immunostimulatory DCs.[40,41] In addition, class II DAMPs, via activation of the NLRP3 inflammasome in cooperation with class I DAMPs, contribute to the shaping of adaptive immunity via the creation of an inflammatory *milieu* that is generally regarded as a necessary condition for full activation of DCs. As reviewed, one obvious link between NLRP3 inflammasome and adaptive immunity is the key cytokine IL-1β which enhances expansion and survival of T cells, promotes differentiation of potentially pathogenic Th17 cells and can promote APC migration, thereby potentially enhancing antigen presentation.[28] Moreover, class III DAMPs (such as MHC class I chain-related proteins A and B), exposed on stressed cells can assist in DC maturation via recognition by the activating receptor natural killer group 2 member D on innate lymphocytes such as natural killer (NK) cells. Interestingly, the bi-directional crosstalk between DCs and NK cells during immune responses has been clearly elucidated. An intense crosstalk between these two cell types not only results in the development of an efficient innate

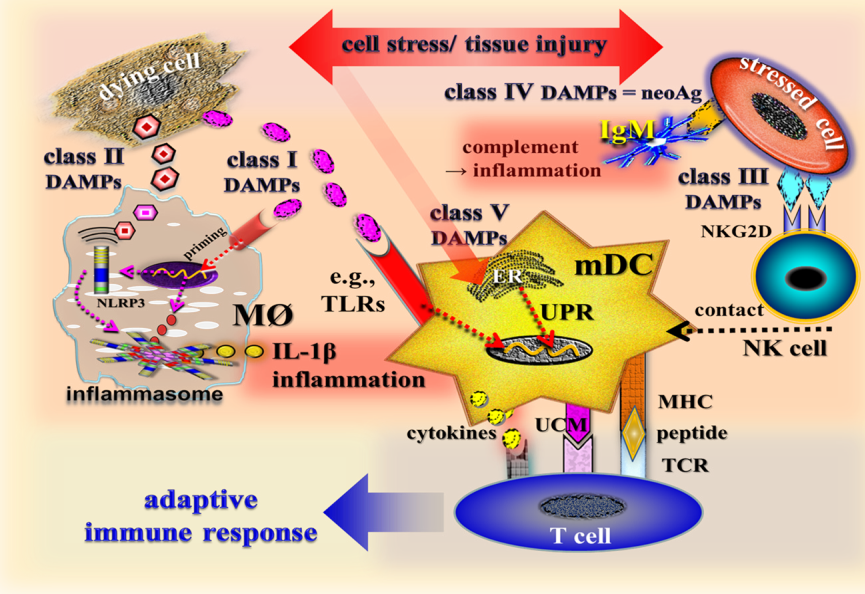

Figure 4: Simplified model depicting the role of five classes of DAMPs in the maturation/activation of immunostimulatory DCs to migrate to secondary lymphoid tissue and induce an adaptive T cell immune response.

DAMPs = damage-associated molecular patterns; DCs = dendritic cells; neoAg = neo-antigens; IgM = immunoglobulin M; NKG2D = natural killer group 2 member D; mDC = mature DC; ER = endoplasmic reticulum; NLRP3 = nucleotide-binding oligomerisation domain-like receptor-containing pyrin domain 3; TLRs = Toll-like receptors; MØ = macrophage; UPR = unfolded protein response; IL-1β = interleukin-1-beta; NK = natural killer; MHC = major histocompatibility complex; UCM = upregulated costimulatory molecules; TCR = T cell receptor.

response through DC-mediated NK cell activation, but also a potent adaptive immune response through NK-mediated DC editing and maturation.[42]

In addition, class IV DAMPs in terms of injury-induced neo-antigens/neo-epitopes contribute to DC maturation via activation of the complement cascade. As shown in a study on reperfusion injury models, one possible trigger mechanism leading to activation of the complement cascade is the binding of autoreactive natural immunoglobulin M antibodies to these neo-epitopes.[43] As so far detected, these oxidation-specific neo-epitopes include non-muscle myosin heavy chain IIA (NMHC-II), actin cytoskeleton and phosphocholine of oxidised phospholipids and malondialdehyde.[44–46] In fact, injury-induced complement activation may contribute to the generation of immunostimulatory DCs mainly through the classical, alternative and lectin pathways. Via the terminal products, the complement fragments C5b-9, known as the complement membrane attack complex, via its lytic action, aggravates cell and tissue injury, thereby increasing the induction of class I, II and III DAMPs and, thus, indirectly contributing to DC maturation.[47] Via the small fragments C3a and C5a, the activated complement cascade contributes to the creation of tissue inflammation. Interestingly, in studies on murine and human DCs, the complement fragment C5a was shown to render iDCs competent for inflammatory cytokine production under non-infectious conditions.[48] Moreover, via the small fragments C3a and C5a released during the course of complement activation, human iDCs have recently been demonstrated to undergo phenotypic maturation as well as functional modulation.[49] These observations suggest a more direct action of the activated complement cascade on the generation of immunostimulatory DCs. Finally, some evidence has been reported suggesting that class V DAMPs associated with ER stress, under involvement of the regulator XBP1, contribute to DC maturation and activation induced by HMGB1.[37,39]

Altogether, these various DAMP-induced scenarios are involved in the pathogenesis of many human diseases. For this reason they are outlined in this two-part review in more detail. Two examples of autoimmune diseases will be discussed at first since they represent a typical paradigm of the intimate interplay between innate and adaptive immune responses.

Autoimmune Diseases

The ability of DAMPs to shape adaptive immunity has been impressively documented in human autoimmune diseases. In the presence of altered-self antigens, DAMPs instigate DC-driven innate immune pathways that promote adaptive autoimmune responses which manifest as severe clinical symptoms; this may also

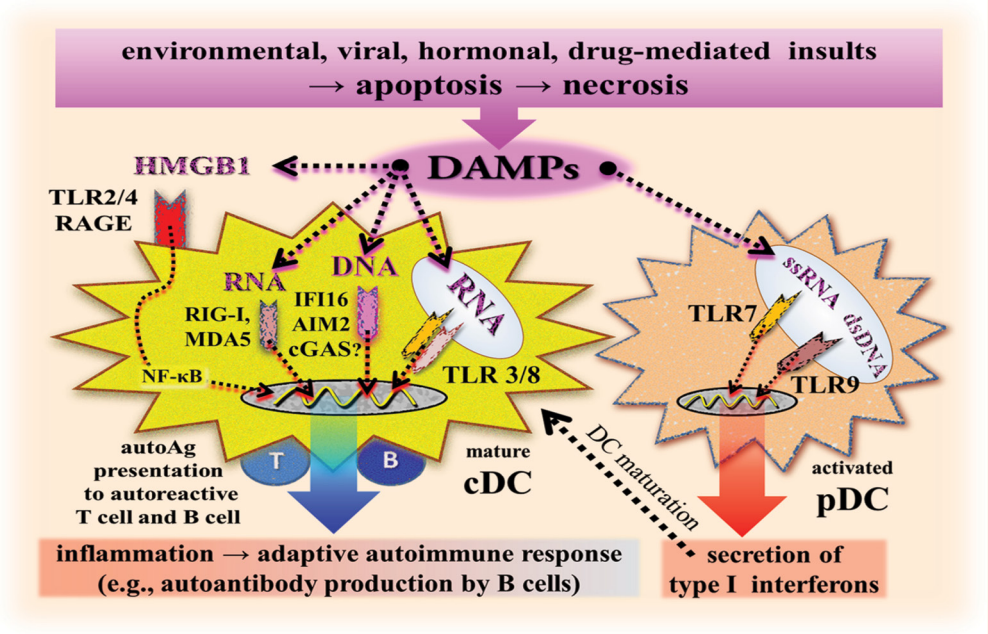

Figure 5: Simplified model of the role of DAMPs as well as the distinct roles of cDCs and pDCs in SLE.

DAMPs = damage-associated molecular patterns; DC = dendritic cell; cDC = conventional DC; pDC = plasmacytoid DC; HMGB1 = high-mobility group box 1; TLR = Toll-like receptor; RAGE = receptor for advanced glycation end-products; RNA = ribonucleic acid; ssRNA = single-stranded RNA; RIG-I = retinoic acid inducible gene I; IFI16 = interferon gamma-inducible protein 16; AIM2 = absent in melanoma 2 protein; MDA5 = melanoma differentiation-associated gene 5; cGAS = cyclic guanosine monophosphate-adenosine monophosphate synthase; dsDNA = double-stranded DNA; NF-κB = nuclear factor kappa B; autoAg = auto-antigen.

be compared in Figure 4. These disorders comprise numerous and diverse pathologies from organ-specific disorders, such as multiple sclerosis and type 1 diabetes, to systemic autoimmune manifestations, such as systemic *lupus* erythematosus (SLE) and RA.

SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is a complex autoimmune condition in which autoantibodies against nucleic acids (for example, dsDNA) and associated proteins in concert with IFNs, trigger immune-complex-mediated inflammation that results in organ damage. Multifactorial stimuli are considered triggers, including environmental insults such as smoking, ultraviolet radiation, viral infections, hormonal imbalances and drug-mediated insults. These promote and precipitate SLE in a genetically predisposed individual. Notably, most of those insults are mediated by uncontrolled oxidative stress that contributes to functional oxidative modifications of cellular protein, lipid and DNA; consequently, this oxidative modification plays a crucial role in immunomodulation and triggering the autoimmune process.[50,51]

Several lines of experimental and clinical evidence support the notion that oxidative stress-related injuries are manifested by a disturbed clearance of apoptotic cells as a consequence of a defect in the recognition and phagocytosis of apoptotic cells, their subsequent accumulation being instrumental in the development of SLE.[51,52] Insufficiently cleared apoptotic debris then leads to secondary necrotic changes associated with the release of neo-epitopes such as dsDNA. Importantly, these autoantigens simultaneously act as host DAMPs, mostly in the form of immune-protein complexes such as HMGB1, cytosolic self-dsDNA and self-RNA. It has been suggested that the excessive release of intact nucleosomes could be the source of those DAMPs.[52–56]

Numerous studies, including experiments on cell lines and in mouse knockout systems, have shown that various receptors of the TLR, NLR, RLR and ALR families are involved in the pathogenesis of SLE, via sensing key SLE-eliciting DAMPs (i.e. HMGB1 and self-nucleic acids). These studies demonstrate that this occurs by the promotion of inflammation and DC maturation, which thereby elicit an autoimmune response [Figure 5].[19–21,55–60] Remarkably, recent findings from experiments in mice and *in vitro* studies on human monocytes have provided evidence that also suggest a role of the NLRP3 inflammasome in the pathogenesis of *lupus*. It has been particularly demonstrated that self-dsDNA together with its autoantibodies induces IL-1β production.[61–63]

Of note, DAMPs involved in SLE (such as cytosolic dsDNA in terms of DNA-immune complexes, but also RNA and HMGB1), in cooperation with signalling pathways leading to NF-κB activation, have been shown to generate potent immunostimulatory human

DCs that elicit strong adaptive immune responses.[64] In fact, innate immune events in SLE induced by the aforementioned DAMPs are translated by PRR-bearing DCs into the adaptive autoimmune response that is typical for this disease. On one hand, self-nucleic acid DAMPs-activated conventional dendritic cells (cDCs) not only produce pro-inflammatory cytokines and chemokines, but also possess a potent ability to present antigens to autoreactive T cells, thereby leading, for example, to autoantibody production by B cells.[64–67] On the other hand, another category of DCs, the plasmacytoid DCs, after sensing self-nucleic acid DAMPs by TLR7 and 9, promote the production of antinuclear autoantibodies and type I IFNs, which are both correlated with the severity of SLE. In fact, increasing evidence suggests that pDCs are essential for the initiation of the abnormal innate immune responses that lead to systemic SLE autoimmunity. It is likely that this occurs through the promotion of cDC maturation and a high production of type I IFNs.[66–69]

RHEUMATOID ARTHRITIS

RA is a chronic inflammatory autoimmune disease of the synovial joints and the surrounding connective tissue. Untreated, the disease can cause cartilage destruction, bone erosion and tendon fracture, leading to the deformation and dysfunction of joints. In addition to disability and a decreased quality of life, RA is associated with reduced life expectancy due to comorbidities and complications, most commonly from accelerated atherosclerosis. Many different cell populations in the RA joint secrete cytokines and other inflammatory mediators, which contribute to pathogenesis. Macrophages are considered a major effector of synovitis, secreting cytokines including tumour necrosis factor IL-1 and -6. In this disease, genetics, epigenetic modifications and environmental factors such as infections and smoking interact and culminate in the production of specific polyclonal autoantibodies including rheumatic factor (directed against the Fc region of immunoglobulin G molecules), anticitrulline protein antibodies and anti-carbohydrate antibodies.[70–74]

There is now ample evidence suggesting that, in RA patients, complex DAMPs-induced events mediated by PRR-bearing innate immune cells are involved in joint inflammation and the formation of these autoantibodies.[75–78] Various TLRs expressed on blood monocytes, synovial fibroblasts or macrophages from synovial fluid from patients with RA have been implicated as potential contributors in the pathogenesis of RA, including TLR2 and 4 as well as endosomal TLR3, 7 and 9.[75–78] Furthermore, a recent study found evidence of modulation of the NLRP3-inflammasome in patients with RA, pointing to the broad spectrum of innate immune machineries operating in the pathogenesis of rheumatoid diseases.[79]

The question remains regarding what types of insults elicit DAMPs and potentially promote joint inflammation and autoantibody formation in RA. There is increasing data supporting the notion that both microbe-mediated infectious and sterile tissue damage evoke DAMPs that function as contributors to the persistence of joint inflammation and the progression of joint destruction after recognition by TLRs. These include HSP22, 70 and the 90 family member, glycoprotein-96, as well as HMGB1 and biglycan.[77,80–85] Moreover, RNA released by necrotic synovial fluid cells from patients with RA has been shown to activate endosome-located TLR3 on cultured RA synovial fibroblasts.[86]

Outlook

The discovery of the danger/injury model has led to modern notions about the human immune system, revealing that it does not always attack and destroy the non-self *per se*. In contrast, the immune system has a strong interest in preserving the 'non-self' provided it is beneficial and does not cause harm.[87] This function, together with the rigorous intention of an immune response to choke off and/or repair any tissue injury—including even the slightest intra- or extracellular perturbation on a molecular level (such as an abnormal accumulation of proteins in the ER)—serves one unique objective: to maintain and restore the homeostasis of an organism. However, there is another side of the coin, which is that uncontrolled exaggerated responses of the immune system can lead to inflammatory collateral tissue damage and some forms of autoimmunity and autoinflammatory diseases. The delicate balance therefore required is the result of complex cellular, humoural and biochemical interactions. The form, concentration and function of the various classes of DAMPs are apparently not only involved in maintaining this balance but can even promote a catastrophic imbalance leading to pathologies.

Furthermore, another layer of complexity is added by the fact that homeostatic danger signals (class V DAMPs) are increasingly suspected of playing a crucial role in the ER stress-induced UPR. In fact, the author of this review article proposes that, as similarly discussed in the context of microbial/viral-triggered ER stress elsewhere, all ER stress-associated perturbed molecular patterns (including sterile) are detected by three sensor molecules—PERK, IRE1α and ATF6—thereby inducing an UPR.[88,89] This stress response

represents an integral part of innate immunity-regulated transcription programmes in terms of a continuous crosstalk with other DAMPs-induced and PRRs-controlled defence machineries, such as the NLRP3 inflammasome. In light of the danger/injury model, innate sensing of any infectious or sterile injury appears to always be associated with a UPR that, in a hierarchical sense, may either be secondarily activated by initial PRR-controlled pathways (e.g. TLR-triggered) or may primarily activate other innate immune pathways (inflammasome-dependent or -independent) to combat dangerous life-threatening conditions.[88] These pathways in commission of the innate immune system are not necessarily exclusive, but may cooperate under orchestration of the various classes of DAMPs to ultimately promote and boost vigorous full-scale inflammatory and immune responses needed to maintain and restore homeostasis.

However, as already stressed above, when uncontrolled, these pathways may lead to pathologies. In fact, the scenario of cell stress/tissue injury-induced innate immune pathways in terms of UPR-PRR-inflammasome synergism, as has been briefly outlined above, is pathologically implicated in many human diseases, including atherosclerosis, metabolic and neurodegenerative disorders, cancer and infection.

Conclusion

This review identified five classes of cell stress/tissue injury-induced DAMPs and discussed the relationship between innate and adaptive immune responses in SLE and RA. The discovery of the crucial role of DAMPs in the pathogenesis of human autoimmune diseases has recently attracted considerable research interest. The interplay between the innate and adaptive immune system has stimulated strong interest in developing new treatment modalities for autoimmune diseases. Either distinct DAMPs of interest or components of PRR signalling pathways appear to be highly relevant targets for new treatment options for those with autoimmune diseases. Of course, concerns will always be raised over targeting molecules executing vital key functions within the innate immune system responsible for the maintenance of homeostasis. Solving these concerns will be a critical objective of future research work.

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