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Myeloid cells in sensing of tissue damage

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Highlights (in a separated editable file)

- Tissue damage recognition by myeloid cells shapes immune responses
- Recognition of immunogenic cell death by myeloid cells promotes inflammation
- Myeloid sensing of tissue damage may also dampen further injury by immunopathology

Keywords

Myeloid cells, tissue damage, immunogenic cell death, disease tolerance.

Abstract

Myeloid cells are components of the innate immune system that represent the first line of defense. Tissue damage, associated with pathological conditions such as infection, cancer or autoimmunity, leads to the exposure of the intracellular content to the extracellular environment. Myeloid cells detect ligands exposed or released by dead cells through specific receptors that signal for a diversity of responses. Inflammatory responses triggered by myeloid cells after sensing tissue injury can contribute to resolution of the damage. The signaling response following dead-cell sensing by myeloid cells can contribute either to an inflammatory or a regulatory response. We review herein some representative examples of how myeloid cells react to the recognition of cell death during specific tissue damage contexts. A deep understanding of the cellular and molecular mechanisms underlying these processes would allow to improve therapeutical interventions in pathologies associated with tissue damage.

Introduction

The structural integrity of a tissue may be compromised due to an infection, trauma or any other inflammatory process. Because of this damage, tissue homeostasis is altered, impacting on its performance. At the cellular level, the injury can trigger Accidental Cell Death (ACD) such as necrosis or Regulated Cell Death (RCD) mechanisms such as pyroptosis or necroptosis [1,2]. In any case, the ultimate consequence of all these phenomena is cell death and the exposure and release of intracellular content to the extracellular environment.

All mammalian tissues are surveilled by myeloid cells including monocytes, macrophages, granulocytes and dendritic cells (DCs). This myeloid compartment patrols the surroundings, ready to sense and react against both infectious and sterile challenges. These cells express germline-encoded pattern recognition receptors (PRRs) that allow the recognition of molecular traits emerging during those insults. These factors are defined as Pathogen-Associated Molecular Patterns (PAMPs) when coming from infectious agents or Damage-Associated Molecular Patterns (DAMPs) if they are of self-origin [3]. DAMPs (also referred to as alarmins) are intracellular components either cytosolic or nuclear, which are thus protected within the plasma membrane, being exposed or released upon tissue damage [4].

The relevance of DAMPs sensing was first proposed by Polly Matzinger in the “Danger theory” [4]. It allowed to explain how immune responses are triggered in the apparent absence of microbial insults, by recognizing these endogenous danger signals. Interestingly, the consequences of this recognition can be a double-edge sword with either inflammatory or regulatory/tolerogenic outcomes. Herein, we will review some examples of the outcomes of tissue damage recognition, and how we could harness these processes to achieve clinical benefits in conditions associated with tissue damage, such as infection, cancer or autoimmunity.

Inflammatory sensing of tissue damage

Sensing of tissue damage can trigger potent inflammatory responses that can induce immunity. This inflammatory cell death has been particularly characterized in the context of antitumor treatments and is mediated by myeloid cells such as DCs [5]. Local chemo- and radiotherapies in cancer kill tumor cells based on their high metabolic and proliferative activities but can also lead to abscopal effects that result in shrinkage of distant tumors, implicating a systemic anti-tumor response. Certain forms of tumor cell death may expose or release DAMPs that are sensed by infiltrating myeloid cells, triggering an inflammatory response against the tumor. This process may overcome the immunosuppressive microenvironment generated within tumors to evade immunosurveillance. Therefore, there is an intense effort to identify and boost cancer therapies that drive immunogenic cell death because of the double benefit of these treatments, with many approaches reaching clinical trials [6]•.

DNA sensing

The StimulaTor of INterferon Genes (STING) is a sensor of cyclic-GAMP produced by cGAS upon binding to intracellular DNA. STING activation stimulates the production of type I interferon (IFN-I) [7]. Notably, IFN-I is required for efficient antitumor CD8⁺ T cell responses [8,9]. In this sense, STING is critical for inducing inflammatory responses against grafted tumors, as STING-deficient mice lack tumor-specific cytotoxic T cells and are unable to control tumor growth [10]••. The driver of these responses is the STING-mediated recognition of tumor DNA by myeloid cells, where STING signaling promotes tumor antigen cross-presentation [10,11]••. Supporting the protective role of DNA release associated with tumor cell death during radiotherapy, the efficacy of irradiation-based treatments in immunogenic tumors relies on the STING-dependent IFN-I production by tumor infiltrating myeloid CD11c⁺ cells [12]. Furthermore, chemotherapies also activate the STING pathway, inducing features of immunotherapy response such as PD-L1 expression [13]. These results support the use of STING agonist as cancer therapeutics to activate antitumor immune responses [14,15].

During tissue injury, mitochondrial DNA (mtDNA) is also released extracellularly as a pro-inflammatory DAMP [16] that is primarily recognized by the endosomal Toll-Like Receptor 9 (TLR9) upon phagocytosis by myeloid cells [17]. The relevance of extracellular mtDNA recognition by myeloid cells through TLR9 has been shown in pathologic conditions as diverse as Inflammatory Bowel Disease (IBD) [18], Systemic Inflammatory Response Syndrome (SIRS) [17] or tissue injury due to endotracheal intubation [19]. In addition, upon access of mtDNA to the cytosol, intracellular receptors such as STING [20] or the NLRP3 inflammasome [21] can also sense mtDNA. These data illustrate how, beyond the proposed therapeutic applications for STING agonists in cancer immunotherapy, the intracellular recognition of cell-free nucleic acids released during tissue damage may show a dark side: chronic inflammation and autoimmunity [22].

In fact, the inflammatory capacity of DNA sensing is tightly regulated during homeostasis, in order to maintain cytosolic self-DNA levels under the threshold of receptor activation in myeloid cells, preventing the occurrence of autoimmunity. Thus, a number of cytoplasmic nucleases are in charge of the cleavage and clearance of unwelcome cytoplasmic DNA, such as TREX1, DNaseII, RNaseH2 and SAMHD1 [23]. The accumulation of cytosolic DNA due to loss-of-function mutations of these enzymes leads to the development of autoimmune type I interferonopathies [24]•. For instance, Aicardi–Goutières syndrome (AGS) is a systemic inflammatory disease with severe neurological manifestations that is caused by TREX1 mutations, with TREX1-deficient mice showing a similar pro-inflammatory phenotype [25]. Interestingly, a concomitant cGAS deletion in these mice reverts the autoimmune disease [25], indicating the relevance of DNA sensing and the potential therapeutic application of its inhibition for treating these type of pathologies.

Nuclear proteins

DNA is not the only pro-inflammatory trait that released during tissue injury (Figure 1, left oval). High mobility group B1 (HMGB1) is a DNA-binding nuclear protein with important structural roles in the assembly of nucleoprotein complexes [26]. But HMGB1 can also promote autophagy when translocated to the cytosol [27].

Importantly, necrotic cells release HMGB1 to the extracellular medium while apoptotic cells do not [28], indicating an specific role of HMGB1 as a DAMP during tissue damage conditions. This alarmin is recognized by different PRR expressed in myeloid cells such as the Receptor for Advanced Glycation End products (RAGE) or the TLR2 and TLR4. HMGB1 recognition activates downstream signaling pathways to promote the production of proinflammatory $\text{TNF}\alpha$, IL-1/-6 or CXCL2, among others [29] and can also promote antigen processing and cross-presentation when binding to TLR4 [30]. Mirroring what happens for DNA recognition, HMGB1 inflammatory sensing can be exploited therapeutically but can also show detrimental effects [31]. For instance, docetaxel chemotherapy induces the release of HMGB1 from dying tumor cells in non-small cell lung cancer (NSCLC) patients, which, in turn, activates infiltrating myeloid CD11c^+ cells [32]. However, a detrimental pro-inflammatory activity of HMGB1 during conditions of tissue damage has been described in a number of pathologies such as hepatic obstruction [33], spinal cord injury [34] or LPS-induced lung injury [35]. This has motivated the study of the HMGB1 inhibitor glycyrrhizin to improve the outcome of tissue damage-related pathologies such as stroke [36] or radiation-induced acute lung injury [37]. In addition, activated myeloid cells actively secrete HMGB1 [38], establishing an auto/paracrine feedback-loop to reinforce the pro-inflammatory reaction to tissue damage. This circuit is relevant in Chronic Obstruction Pulmonary Disease (COPD). In this pathology, the congested lung tissue releases HMGB1. Of note, patients suffering COPD cannot clear efficiently the ubiquitous fungal pathogen *Aspergillus fumigatus*, which induces the production of further HMGB1 by myeloid alveolar macrophages, perpetuating the inflammatory state [39].

Another nucleoprotein released during accidental cell death is the spliceosome-associated protein 130 (SAP130). This DAMP binds to the C-type Lectin Receptor (CLR) MINCLE/CLEC4E expressed by myeloid cells, promoting the recruitment of neutrophils to the site of tissue damage [40]. The pro-inflammatory role of MINCLE in recognition of endogenous ligands (including SAP130 [40] and β -glucosyl-ceramide [41]) has been described in a number of tissue-injury related conditions such as subarachnoid hemorrhage [42], alcohol-induced hepatic injury [43], Crohn's disease [44], multiple sclerosis [45] and acute kidney injury [41].

Nuclear histones are also alarmins released during tissue damage conditions occurring upon a number of acute critical illnesses [46]. Histones are recognized in the extracellular environment by myeloid cells, mostly through TLR4 [47], leading to pro-inflammatory immune responses. These responses can be further boosted in certain conditions. *Streptococcus pyogenes* infection generates necrotizing lesions of soft tissues, where histones are released as DAMPs. At the same time, the bacteria produces the Streptococcal Inhibitor of Complement (SIC) virulence factor that binds to histones. Histones, similar to anti-microbial peptides, show some anti-bacterial activity [48,49], which is dampened by SIC binding [50]; however the pro-inflammatory activity of histones and their associated DNA is boosted upon SIC binding compared with free extracellular histones [50]. Interestingly, the pro-inflammatory activity of histones is also boosted when they are recognized in concert with other DAMPs.

Combined pro-inflammatory sensing of nuclear DAMPs

Although the triggering of some immunogenic cell death programs such as necroptosis or pyroptosis is well regulated at the molecular level [1], the eventual consequence of this death processes is the disruption of the cell integrity and the release of a massive “cocktail” of intracellular matter. In this scenario, it is expected that a mix of DAMPs, rather than a single one, drive immunogenic responses. This is the case, for instance, for the already introduced inflammatory effect of HMGB1 and DNA sensing by myeloid cells. Both intracellular components contribute separately to inflammation upon cardiac ischemia-reperfusion through RAGE and TLR9, respectively [51]. However, under similar settings (hepatic ischemia-reperfusion), TLR4 is the critical receptor for HMGB1 recognition with an equivalent contribution of TLR9 by sensing DNA bound to histones [52].

But these DAMPs can also work in a cooperative manner. During autoimmune responses in lupus, there is a mutual interaction between HMGB1 and DNA, as complexes of both components augment the binding of HMGB1 to RAGE, boosting in turn TLR9-mediated inflammatory responses [53]. Binding of nucleic acids to HMGBs may be a precondition for the recognition by and activation of TLR, RLR and cytosolic nucleic-acid receptors [54]. In fact, this mechanism driven by HMGB1 has been

proposed to play a role in the severe pulmonary inflammation occurring at late stages of COVID-19 [55]. In a similar way, histones released upon cell death are recognized by the CLR CLEC2D, transferring them to endosomal compartments where histones-bound DNA triggers TLR9-mediated inflammatory responses [56]●●.

Regulation of inflammation by sensing tissue damage

During most of the conditions described before, the recognition of DAMPs by myeloid cells triggers direct inflammatory responses by activating signaling pathways downstream certain PRRs. However, the sensing of tissue injury is not always inflammatory but can rather regulate inflammation (Figure 1, right oval). Under these circumstances, the sensing of tissue damage through specific sensors dampens inflammatory responses triggered by heterologous receptors in the same cell. These regulatory responses to tissue damage can dampen the recruitment of pro-inflammatory populations such as monocytes or neutrophils that may contribute to tissue damage.

This is the case for the detection of filamentous actin (F-Actin) by the CLR DNGR-1/*CLEC9A* [57,58], reviewed in [59]. F-Actin is sheltered intracellularly in healthy cells, but exposed to the extracellular medium when the cell membrane is disrupted. F-Actin recognition by DNGR-1 mediates cross-presentation of dead cells-associated antigens following Vaccinia virus (VACV) or Herpes Simplex Virus (HSV) infection [60–62]. However, under both sterile (caerulein-induced pancreatitis) and infectious (systemic *Candida albicans*) conditions running with massive local tissue damage, DNGR-1 expressed in dendritic cells dampens the infiltration of neutrophils that contribute to immunopathology. Thus, upon those conditions, DNGR-1-deficient mice show exacerbated tissue injury due to an overwhelming presence of infiltrating neutrophils. Mechanistically, DNGR-1 engagement activates the phosphatase SHP-1; this phosphatase inhibits the activation of heterologous receptors expressed in the same dendritic cell, receptors which are involved in the ignition of pro-inflammatory responses [63]●●.

Of note, the detrimental effect found in the absence of DNGR-1 was not coupled to an increase in pathogen burden during *Candida albicans* infection [63]. This effect is reminiscent of the “disease tolerance” process. This protective mechanism implies the activation of regulatory immune responses during infections, in order to reduce self-inflicted immune tissue damage without affecting pathogen load [64]•.

Paradoxical regulatory responses of tissue damage receptors

The negative regulation of neutrophil infiltration under sterile tissue damage conditions was also described for another myeloid CLR, CLEC12A/CLL-1 [1]. In this case, monosodium urate (MSU) crystals are the recognized DAMPs. Thus, CLEC12A-deficient mice showed elevated peritoneal neutrophil numbers after injecting dead cells, or in the thymus after sublethal total body irradiation [65]•. However, depending on the context, the immune consequences of tissue injury recognition by myeloid cells and their receptors can be paradoxical. For instance, antibody-mediated blockade of CLEC12A reduced the myeloid infiltration into the central nervous system during an experimental multiple sclerosis model [66]. This apparently contradictory role for CLEC12A in different settings may be explained by its amplifying role of type-I interferon (IFN-I) responses [67]. Therefore, the balance between regulatory and pro-inflammatory responses after sensing tissue damage can be tuned depending on the predominant immune response [68].

Thus, some DAMPs, mostly thought to be pro-inflammatory can also trigger regulatory responses (Figure 1, overlapped ovals). This is the case for the recognition of SAP130 by MINCLE, previously defined as pro-inflammatory. However, pancreatic ductal adenocarcinoma cells release SAP130 by a necroptosis-mediated mechanism. The recognition of this nucleoprotein by MINCLE in this tumor setting contributes to an immunosuppressive program in cancer infiltrating myeloid cells, favoring tumor growth. In fact, MINCLE ligation by exogenous Trehalose-6,6-dibehenate (TDB) administration recapitulates this immunosuppressive phenotype, accelerating pancreatic oncogenesis [69]••. This divergent inflammatory outcome may be related to a diverse signaling pathway triggered downstream the receptor under different conditions. Indeed, MINCLE ligation by a ligand derived from *Leishmania major* couples

the receptor to SHP-1 signaling, triggering an inhibitory ITAM configuration that regulates activating signals triggered by heterologous receptors [70].

Sensing of HMGB1 can also have regulatory properties. This alarmin binds to the membrane-anchored glycoprotein CD24; this complex is recognized by Siglec-10 in the mouse or its human homolog Siglec-G, delivering regulatory signals that dampen the pro-inflammatory activity of HMGB1 in dendritic cells. Thus, in a model of acetaminophen (AAP)-induced liver necrosis, both CD24- and Siglec-10-deficient mice show exacerbated HMGB1-mediated inflammation and worse survival than wild-type counterparts [71]. Interestingly, the Siglec-G-mediated regulatory signals in response to HMGB1 may also regulate T cells, modulating the severity of graft-versus-host disease (GVHD) [72]. Therefore, to have a whole picture of the inflammatory response triggered after the sensing of tissue damage, it is also important to understand the composition of the immune infiltrate and their coordinated responses.

Conclusions

Tissue injury conditions lead to massive release of different DAMPs. As discussed in here, the recognition of this tissue damage by myeloid cells can generate both pro-inflammatory and regulatory responses. Understanding the molecular mechanisms that govern these differential responses is critical to harness them in pathological situations such as cancer, chronic inflammation or autoimmunity. There are still open questions on what determines the activating or regulatory outcome; Is it conditioned by the PRR expression profile of surrounding cells? How do all those signals integrate? In addition, some of these tissue damage conditions are a consequence of infections, where pathogens also provide PAMPs, increasing the complexity of the response. The unbiased global study while, at the same time, we dissect the diversity at the single cell level may increase our understanding of this fascinating field of tissue damage sensing.

Author contributions

Conceptualization: Cdelf and DS. Writing original draft: Cdelf. Writing review and editing: Cdelf and DS. Funding acquisition: DS.

Figure legend

Figure 1. Inflammatory and regulatory functions of myeloid receptors and DAMPs compiled in this review. Upon tissue damage conditions, dead cells release DAMPs (in *italic* in the chart) that can be recognized by receptors expressed in myeloid cells. This recognition triggers either inflammatory (left oval) or regulatory (right oval) responses. Some of these receptors can work simultaneously (dashed lines) as dying cells do not release isolated DAMPs but a mix of them. Of note, some of these DAMPs such as HMGB1 or SAP130 can trigger both inflammatory and regulatory responses depending on the context.

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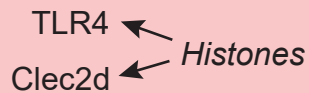
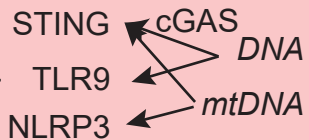
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INFLAMMATORY



REGULATORY

