DAMPs and Innate Immune Training

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The ability to remember a previous encounter with pathogens was long thought to be a key feature of the adaptive immune system enabling the host to mount a faster, more specific and more effective immune response upon the reencounter, reducing the severity of infectious diseases. Over the last 15 years, an increasing amount of evidence has accumulated showing that the innate immune system also has features of a memory. In contrast to the memory of adaptive immunity, innate immune memory is mediated by restructuration of the active chromatin landscape and imprinted by persisting adaptations of myelopoiesis. While originally described to occur in response to pathogen-associated molecular patterns, recent data indicate that host-derived damage-associated molecular patterns, i.e. alarmins, can also induce an innate immune memory. Potentially this is mediated by the same pattern recognition receptors and downstream signaling transduction pathways responsible for pathogen-associated innate immune training. Here, we summarize the available experimental data underlying innate immune memory in response to damage-associated molecular patterns. Further, we expound that trained immunity is a general component of innate immunity and outline several open questions for the rising field of pathogen-independent trained immunity.

Keywords: DAMP, trained innate immunity, heme, vimentin, oxLDL

INTRODUCTION

Monocytes and macrophages (Mφ) are professional phagocytic cells (1), a feature first described by Elie Metchnikoff almost 150 years ago (2). Circulating monocytes originate from the bone marrow and can differentiate into monocyte-derived Mφ and dendritic cells upon stimulation (3, 4) and subsequently elicit a robust inflammatory response, which includes the secretion of cytokines. This qualifies these cells as initiators of inflammation and places them in the first line of defense against invading pathogens (3, 5). In contrast, tissue resident Mφ, derived from the yolk sac or the fetal liver, are thought to regulate organ development and homeostasis as well as to control resolution of inflammation (5, 6). However, this is not a fixed dichotomy and under specific conditions, monocyte-derived Mφ can also acquire a phenotype that promotes homeostasis and tissue repair similar to tissue-resident Mφ (5).

In contrast to adaptive immunity that develops antigen-specific memory, the cellular components of the innate immune system, including monocytes and Mφ, were long thought not to remember previous stimulation. Instead after a transient phase of recovery, it was assumed that they would react in a similar and repetitive way to inflammatory stimuli (7).
MEMORY OF THE INNATE IMMUNE SYSTEM

The above-described perspective was challenged during the last 15 years by several independent discoveries that showed persistent histone modifications in Mφ in response to the bacterial cell-wall component Lipopolysaccharide (LPS), the fungal cell wall component β-1,3-D-glucan among others (8–10). The phenomenon of acquired and persistent alterations of innate immune responses was coined as innate immune memory and presents typically as tolerance, referring to a reduced response or trained immunity (TRIM), referring to an enhanced response upon restimulation (10).

The first observation that LPS-mediated Toll-like receptor (TLR)-signaling induced gene-specific chromatin modifications were made by Foster et al. when aiming to understand immunotolerance (8). The authors revealed a set of gene-specific chromatin modifications that are associated with gene silencing or enhanced response to re-exposure (8). In addition, it was established that a subset of genes could be persistently tolerized while others remained unaffected or even had enhanced transcription, the latter set being described as non-tolerizeable genes. Subsequent work by other groups revealed that the fungal cell wall component β-1,3-D-glucan and other inflammatory stimuli can also induce specific and persistent modifications of histone acetylation and methylation, underlying a long-term modulation of the innate immune response (Figure 1) (9, 11). Both phenomena share common characteristics, e.g., exposure to a given stimuli ensues long-term modulation of the innate immune response to that same or related stimuli and are associated with long-term modification of gene transcription (8, 9). TRIM in vivo and in vitro was first demonstrated using the fungal cell wall component of Candida albicans β-1,3-D-glucan, a bona fide pathogen-associated molecular patterns (PAMP) or the Bacille-Calmette Guerin (BCG) the live-bacteria tuberculosis vaccine (9, 11–13). These molecules commonly use the mechanistic Target of Rapamycin (mTOR) pathway to induce TRIM to activate specific

![Figure 1](Figure 1 | Classical in vitro model of trained immunity. Trained immunity describes a functional, metabolic and epigenetic adaptation of innate immune cells to previous stimuli with ensuing increased immune response, i.e. cytokine release, to secondary stimulation. (A) The classical model applies the Dectin-1 agonist β-1,3-D Glucan as the first stimulus and the TLR-4 agonist LPS as the second stimulus. (B) The basis for β-1,3-D Glucan induced trained immunity are metabolic adaptations, including the mTOR signal-transduction enhanced glycolysis. Interrupted errors indicate that many more proteins are involved in the signaling cascade, which are not depicted in the figure.)
DAMAGE AND DANGER

The prevailing concept since the 1950s that the immune system evolved to distinguish self from non-self was challenged in a seminal essay by Polly Matzinger (27). She proposed that the immune system does not exclusively differentiate between foreign and self but instead evolved to detect cues indicating danger. Matzinger’s danger theory was primarily intended to understand T-cell biology. This theory contains specifically the idea that professional antigen presenting cells are activated “in the presence of tissue destruction” (27). Whether this is a completely novel approach or a reappraisal of earlier thoughts is not the topic of this review (28). According to Matzinger, immune cells are primarily made for sensing detecting danger and only sense invading microorganisms for the reason that infections typically are associated with danger, in the form of cellular stress and damage (27, 29). In the classical concept of immune recognition, DAMPs would in fact be considered as “self”. However, it has become clear that certain host-derived molecules can activate innate immunity and induce an inflammatory response regardless whether they are triggered by infection or by sterile inflammation (30). These molecules have been designated as damage or danger-associated molecular pattern (DAMP) and are also referred to as alarmins by some authors. An overview of the different terminology is shown in Table 1.

Overall, DAMPs are a rather heterogeneous group of molecules with shared common features. They are a) host-derived and not pathogen- or environment-derived and b) induce an innate immune response. In order to acknowledge their heterogeneity, DAMPs have recently been further subclassified as continuous DAMPs (cDAMPs), inducible DAMPs (iDAMPs) (Table 1) (42, 43). In this classification, cDAMPs are intracellular molecules that are not present in the circulation under non-pathological conditions and are set-free without modifications upon cellular damage. iDAMPs are secreted and/or induced molecules, released from dying cells and have been proposed to reflect various stress and damage pathways activated during stress (43). DAMPs are heterogenous in their origin and function. Yet, they induce a rather homogenous sterile inflammation that equally involves cytokine release, neutrophil recruitment and the induction of T-cell immunity equally to the response elicited by PAMPs (30). The recently classified group of lifestyles-associated molecular patterns (LAMP) consist of molecules increased with western lifestyle that induce a sterile inflammation. These are distinct from DAMPs as they cannot be cleared, and if persistent, lead to a chronic inflammation. This group includes cholesterol, monosodium urate or oxidized LDL and others (42) (Table 2).

CONSERVED PATTERN RECOGNITION TO DAMP AND PAMP

Monocytes and Mφ express different sets of pattern recognition receptors (PRRs) that bind to PAMPs (50) and DAMPs (51–53). There are four distinct classes of PRR that are identified so far: Toll-like receptors (TLR), nucleotide-binding oligomerization domain (NOD)-Leucine-rich repeats (LRR)-containing receptors (NLR), retinoic acid-inducible gene 1 (RIG-1)-like receptors (RLR), and the C-type lectin receptors (CLR) (54). Binding of PAMPs and DAMPs by PRRs triggers distinct signaling transduction pathways which elicit the expression of immunomodulatory molecules, e.g. cytokines, indispensable for an appropriate immune reaction against an exogenous or endogenous threat.
TRIM can be induced by different classes of PRRs, as illustrated by β-glucan, which binds to the C-type lectin receptor Dectin-1 activating the noncanonical Raf-1 pathway signaling (12). So far only one intracellular PRR has been identified to result in TRIM upon engagement, namely, NOD-2/Rip2 in response to BCG (11). This is fundamentally different to the immunological tolerance which involves TLR-4 activation and the NF-κB/MAPK pathway (55). We here posit that DAMP-induced TRIM shall not involve cytoplasmatic PRR such as NLR or RIG-1. This is because by definition, a DAMP is an endogenous, i.e. cytoplasmatic or nucleic, molecule that is released in the circulation and then bound by extracellular receptors, with the potential to be endocytosed after ligand-binding (56). In contrast, cell intrinsic stress responses mount conserved stress-control pathways that prevent tissue damage (57). the release of DAMPs and as a consequence also the ensuing activation of the immune system.

DAMPs AS TRainers

Compared to PAMP-induced TRIM, DAMP-induced TRIM is less well studied and understood. Five years ago, Crisan et al. had speculated on the existence of DAMP-induced trained immunity and summarized concepts and early data (58). During the last years, increasing amounts of evidence shows that endogenous molecules promote in fact TRIM include the iron-containing tetrapyrrole heme (22), the intermediate filament vimentin (45), oxidized low-density-lipoproteins (oxLDL) (46) and the mineralocorticoid aldosterone (59). An
overview of the studies is provided in Table 2. As aldosterone is a hormone and not considered a DAMP, it will not be discussed further in this review.

Both heme and vimentin are alarmins that can activate PRR signaling either by TLR-4 or Dectin-1, respectively (37, 38). OxLDLs are a heterogenous group of molecules that, depending on their oxidation status, bind to different PRR. Minimally modified LDL can directly bind to cluster of differentiation (CD)14, TLR-2 and -4 triggering immune activation (48, 60, 61). Further oxidized OxLDL is recognized by a family of scavenger receptors including the lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), CD36 and the scavenger receptor class B type I (SR-BI) (62). In the following paragraphs we will briefly summarize the findings for the individual TRIM-promoting DAMPs.

Heme

Heme is a tetrapyrrole with a central iron atom found in hemoglobin and other hemoproteins. The reactive central core, which is responsible for the biological heme functions can reversibly change its oxidation state from ferric (Fe$^{3+}$) to ferrous (Fe$^{2+}$) to accept or donate electrons, respectively. This reactive core makes heme not only an indispensable molecule for many physiological processes, but it also bears the risk for cytotoxicity when unbound to proteins. As such, heme is able to oxidize lipids and proteins and can induce DNA damage (63, 64). Additionally, heme can promote the generation of free radicals e.g. when reacting with other organic hydroperoxides, further imposing cellular damage (63, 64). Under homeostatic conditions heme production and degradation are tightly controlled processes. Following hemolysis or tissue damage, heme is passively released into the circulation. There it is bound non-covalently by serum scavenger proteins and taken up by Mø (65–70). As far as we know now, there is no active heme export.

With increasing concentrations, the buffering capacity of serum protein becomes exhausted resulting in the accumulation of cell-free, ‘labile’ heme in the plasma (70, 71). This contributes critically to the pathogenesis of severe acute infectious disease, as demonstrated for malaria (72) and for bacterial sepsis (73–75). Labile heme is a pro-type alarmin that is sensed by TLR-4 but also activates the spleen tyrosine kinase (Syk) pathway both inducing cytokine expression, including the cytokines IL-6 and IL-1β in innate immune cells (37, 76). As heme synergized with LPS with regards to cytokine release, it was assumed that heme would bind to a distinct pocket of TLR-4 and specifically induced MyD88 signaling (77). How heme triggers Syk signaling is currently unknown (37, 76, 78). We have recently described that heme is a potent inducer of TRIM which is mediated by the activation of Syk (22). In contrast to other TRIM inducers this is independent of mTOR. However, in vitro heme training causes comparable expansion of myeloid primed long-term hematopoietic stem cells as seen in PAMP-induced TRIM (19, 79).

In line with the above, Schrum et al. identified that damaged red blood cells and hemozoin crystals, as a result of a malaria-inducing Plasmodium falciparum infection, induce TRIM in primary monocytes in vitro (80). Plasmodium spp. replicate in erythrocytes and regularly disrupt their cell membrane to be released into the circulation which is accompanied by the release of the Plasmodium -metabolic byproduct hemozoin (81, 82). This study perceives the Plasmodium induced TRIM to be a result of PAMPs and does not consider that damaged red blood cells as well as hemozoin are major sources of labile heme. Together with the findings of Jentho et al. (22), TRIM seems to be an inherent component of innate immune cells considering the wide range of infections associated to release of labile heme. Given the human-pathogen co-evolution especially with Plasmodium spp. these studies raise the question what kind of evolutionary advantage is achieved by inducing TRIM.

Oxidized LDL

Oxidized LDL encompasses a number of different particles such as protein and fatty acids with varying oxidation states (83, 84). Application of in vitro oxLDL induces TRIM in Mø, as well as in non-hematopoietic lineage cells such as endothelial cells and human coronary smooth muscle cells (46, 48, 49). OxLDL bind to a family of scavenger receptors that include CD36 (62) which in turn can activate TLR-4 and TLR-6 signaling (85). Mechanistically, as seen in β-glucan, oxLDL-TRIM is associated with mTOR signaling, H3K4 methylation and increased glycolysis (46, 86). The same, sensing by TLR and signaling via mTOR pathways are involved in TRIM in vascular smooth muscle cells (48). Potentially this explains why training effects by oxLDL have been shown for non-myeloid tissues that also express the same receptors. In fact, this should also hold true for the other mediators of TRIM, but this, to our knowledge, has not been addressed experimentally.

OxLDL may, however, also be considered in light of the recently suggested concept of LAMPs, which refers to molecules not associated with pathogens or cellular damage but instead arising from “failure-to-adapt-disease” such as observed in the context of atherosclerosis or gout. Key features of LAMPs have been defined as being persistent and having the ability to induce chronic disease (42). Furthermore, oxLDL cannot be cleared by the immune system and consequently induce chronic inflammation (30). We consider this potentially relevant for this topic as acute oxLDL exposure induces TRIM (46, 49), while LAMP-induced TRIM would involve a non-resolved stimulus and persistent activation, with the associated pro-inflammatory phenotype in phagocytes. Whether the observed link between high-fat diet, the predominant factor for the development of atherosclerosis, NLRP-3 inflammasome-dependent induction of TRIM in mice (87) is also mediated by oxLDL signaling is currently unclear.

Vimentin

Vimentin is an intermediate filament protein involved in inflammatory responses and in Mø endocytosis (88). Vimentin is a classical alarmin, sensed by Dectin-1 (38). While investigating donor allografts in a model of heart transplantation Braza et al. showed in the ex vivo second hit model, that isolated Mø exposed to first vimentin and subsequent to HMGB-1 had an enhanced cytokine release of...
ATP for example is rapidly used by the cell and cleared (91). TRIM-inducing DAMPs or their degradation products, whereas it is unclear, at least in the in vitro models, whether Mφ can clear TRIM-inducing DAMPs or their degradation products, whereas ATP for example is rapidly used by the cell and cleared (91).

**CONCLUDING REMARKS**

Over the last 15 years it has become clear that memory is a general feature of innate immunity. Strikingly, DAMP- and PAMP-induced trained immunity show comparable molecular reaction pattern. Recognition of both induce histone modifications and long-term persistent alteration of myelopoiesis that impact on the immune response upon secondary stimulation. This coherence hints towards an evolutionary conserved program, with logical advantages and so far, not understood disadvantages for the host mounting a secondary inflammatory program. Yet, it remains unclear under which conditions it is beneficial and when it is deleterious. This needs to be addressed for future application of the TRIM concept especially if applied in clinical settings.

Several further questions remain to us. Why are certain DAMPs worth remembering while others apparently not? How does DAMP-induced TRIM affect leukocyte trafficking, adaptive immunity, iNKT cell regulation and repair? Especially as damage signaling should result in the induction of a repair response. Is there an intracellular signaling funnel via which this reaction pattern is transmitted or can only DAMPs that can activate extracellular PRR-signaling lead to innate immune training? If intracellular PRR recognize DAMPs and initiate innate immune training, how would a constant immune activation be prevented? And ultimately does an epigenetic imprinting in the myeloid compartment have an evolutionary advantage to defend against pathogens? We are confident that the next years will shed light on some of these questions.

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