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Review Article

How is inflammation initiated? Individual influences of IL-1, IL-18 and HMGB1

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ABSTRACT

Pro-inflammatory cytokines are crucial for fighting infection and establishing immunity. Recently, other proteins, such as danger-associated molecular patterns (DAMPs), have also been appreciated for their role in inflammation and immunity. Following the formation and activation of multiprotein complexes, termed inflammasomes, two cytokines, IL-1β and IL-18, along with the DAMP High Mobility Group Box 1 (HMGB1), are released from cells. Although these proteins all lack classical secretion signals and are released by inflammasome activation, they each lead to different downstream consequences. This review examines how various inflammasomes promote the release of IL-1β, IL-18 and HMGB1 to combat pathogenic situations. Each of these effector molecules plays distinct roles during sterile inflammation, responding to viral, bacterial and parasite infection, and tailoring the innate immune response to specific threats.

1. Introduction

The immune response makes use of soluble factors, ranging from small molecules to large proteins. The best known subset of these soluble factors is cytokines—small, inducible proteins that both promote and sequester inflammation. Cytokines can be released by all cell types. Cytokines are classified into families based on three-dimensional structure and the receptors to which they bind. Dysregulation of these cytokines can lead to excessive inflammation or increased pathology. Control of inflammatory diseases has been sought by neutralizing pro-inflammatory cytokines. There are a wide range of pro-inflammatory cytokines, including interleukin (IL)-1, IL-12, IL-18, IL-23, TNFα. Of these, the IL-1 family contains some of the best studied cytokines, including IL-1, the first discovered cytokine, as well as IL-18 [1]. IL-1 family members typically adopt a β-trefoil conformation [2]. The receptors for IL-1 and IL-18 both contain Toll-IL-1 receptor domains that signal through the adaptor protein MyD88 to trigger NF-KB signaling [2,3]. Interestingly, most IL-1 family members also lack a classical secretion signal, indicating that they are released by alternative mechanisms.

IL-1 was initially identified as the pyrogen responsible for fever [4], which was soon found to be the same protein as the lymphocyte activating factor [5]. Since then, it has been shown that IL-1 initiates many immunologic responses, including fever, prostaglandin synthesis, neutrophil influx and activation, T-cell activation and cytokine production, B-cell activation and antibody production, and fibroblast proliferation and collagen production [1] (Fig. 1). IL-1 is produced by two distinct genes, IL-1α and IL-1β, that both engage the same receptor. IL-1α is constitutively produced in most cell types and can be biologically active without any processing [1,6]. However, Calpain II can process IL-1α, which increases its biological activity [7]. IL-1α can be expressed as a membrane bound form or released from cells during apoptosis or necrosis [2,6,8,9]. Therefore, IL-1α alerts the immune system to general tissue damage.

In contrast to the widespread expression of IL-1α, IL-1β expression is more tightly regulated and most abundantly produced by a

Abbreviations: AIM 2, absent in melanoma 2; ASC, apoptosis-associated speck-like protein containing a caspase activation and recruitment domain; CAPS, cryopyrin-associated periodic syndromes; CARD, Caspase Activation and Recruitment Domain; Casp1, Caspase-1; DAMP, danger-associated molecular pattern; EAE, experimental autoimmune encephalomyelitis; FCAS, familial cold activated syndrome; HMGB1, High Mobility Group Box 1 protein; IAV, influenza A virus; IFNγ, interferon γ; IL, interleukin; KSHV, Kaposi's sarcoma associated herpesvirus; LRR, leucine-rich repeat; MAVS, mitochondrial antiviral signaling protein; NK, natural killer; NLR, Nod-like receptor; NLRC, Nod-like receptor containing a CARD domain; NLRP, Nod-like receptor containing a pyrin domain; PAMP, pathogen-associated molecular pattern; PR3, proteinase 3; PRR, Pattern-Recognition Receptor; PYD, pyrin domain; RAGE, receptor for advanced glycation end products; RSV, respiratory syncytial virus; TLR, Toll-like receptor.

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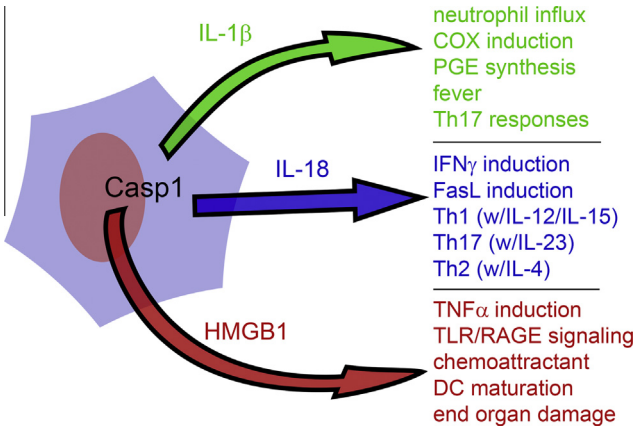

Fig. 1. Downstream effects of cytokine and DAMP release. Following release by the inflammasome, IL-1β, IL-18 and HMGB1 each contribute to distinct downstream immune responses.

subset of professional immune cells—myeloid cells [1]. Unlike IL-1α, IL-1β is synthesized as an inactive pro-form that must be cleaved prior to biological activity [10]. The signal to initiate IL-1β translation is provided by a Pattern-Recognition Receptor (PRR). PRRs are receptors that recognize and respond to specific molecules typically present during infection, inflammation or other pathologic conditions. Although multiple PRRs can promote IL-1β translation, the Toll-like Receptors (TLRs) most commonly provide this priming signal [2]. Following translation, IL-1β is cleaved and released in a regulated fashion from the cell. This processing and release is primarily controlled via the inflammasome (see below). However, other mechanisms exist to promote IL-1β processing and secretion, including proteinase 3 (PR3), matrix metalloproteinases, cathepsin G, elastase and streptococcal pyrogenic exotoxin B [11–14]. Generally, local IL-1β secretion promotes neutrophil recruitment and promotes Th17 differentiation of T-cells [15] (Fig. 1). Th17 differentiation is accomplished in part by the ability of IL-1β to block production of the Th1 cytokine interferon γ (IFNγ) through induction of prostaglandins, which inhibit IFNγ production [14]. Thus, IL-1β alerts the rest of the immune system that innate effectors have recognized a threat.

Although IL-1β can block IFNγ, IL-18, a closely related IL-1 family member, instead enhances IFNγ secretion among other distinct properties. Unlike IL-1β, IL-18 protein is expressed in most cell types as an inactive precursor [3]. This inactive precursor is processed and released through inflammasome activation (see below) as well as by Fas via Caspase-8, PR3, merpin β and granzyme B [16–18]. In contrast to IL-1β, IL-18 does not induce fever or prostaglandin synthesis [19,20]. Although IL-18 does not initiate fever or prostaglandin synthesis, IL-18 promotes inflammation through other mechanisms (Fig. 1). Consequently, neutralization of IL-18 is therapeutic in many murine disease models [3]. However, IL-18 also plays a role in homeostasis, as elimination of IL-18 leads to metabolic syndrome phenotypes in mice [21,22]. IL-18 is best known for its ability to promote the Th1 response through the potent induction of IFNγ, which requires either IL-12 or IL-15 [18] (Fig. 1). Memory responses also require IL-18 [23]. IL-18 is a multifunctional enhancing cytokine that can also enhance other T-cell responses. With IL-23, IL-18 can enhance Th17 responses from lineage-committed cells [10]. When IL-12, IL-15, or IL-23 are absent, IL-18 can instead promote Th2 responses [10,24,25]. Thus, IL-18 is a pro-inflammatory cytokine with distinct properties from IL-1β.

Cytokines like the IL-1 family members are not the only group of pro-inflammatory proteins. Many other proteins can induce innate immunity and inflammation, even though they may not strictly be classified as cytokines. Instead, these proteins are generally considered danger-associated molecular patterns (DAMPs) or alarmins. DAMPs typically possess a non-inflammatory "day job" within the cytosol or nucleus of cells, which cytokines generally do not. Upon release from the cell, DAMPs such as High Mobility Group Box 1 protein (HMGB1) can bind to multiple PRRs and trigger inflammation [26]. In contrast to cytokines, DAMPs typically bind with a lower affinity and lack dedicated receptors [2].

Perhaps one of the best-studied DAMPs is HMGB1. HMGB1 is an abundant non-histone nuclear protein with an important role as a minor-groove binding enhancer [27]. Structurally, HMGB1 is comprised of two basic boxes responsible for DNA binding and a highly acidic C-terminal tail [28]. In its "day job", HMGB1 enhances binding of regulatory proteins to a number of genes, including ones important for regulation of mitochondrial quality control and autophagy [29]. Due to its day job, knockout of HMGB1 in mice is lethal [30]. Once released from the cell, either via necrosis or via the inflammasome (see below), HMGB1 is a potent immunomodulator [27] (Fig. 1). In this way, HMGB1 is similar to IL-1 and IL-18 in that it requires non-classical secretion prior to initiating any inflammation. HMGB1 is perhaps best known for its role as the lethal mediator of late-phase toxicity following endotoxic shock [31]. Similarly, neutralizing anti-HMGB1 antibodies protect mice following ischemia–reperfusion injury [32]. However, conditional ablation of HMGB1 in subsets of cells sensitizes mice to both endotoxic shock and ischemia–reperfusion injury [33,34]. This suggests that HMGB1 can report and exacerbate general cellular damage while also limiting specific damage when used by myeloid cells and specific cell subsets.

In contrast to cytokines, DAMPS bind to a wide range of receptors. The complexity of DAMP activity is exemplified HMGB1. HMGB1 binds to a wide range of receptors, most notably TLR4 and receptor for advanced glycation end products (RAGE) [35]. In many cases, this binding is enhanced or potentiated by binding to a wide variety of other factors, including both pathogen-associated molecular patterns (PAMPs) like lipopolysaccharide and cytokines, including IL-1 [28,35–37]. Although HMGB1 does bind to a wide variety of factors, these are specific, low affinity interactions. For example, HMGB1 does not bind to nor synergize with IL-18 [38]. This wide specificity is further complicated by the modulation of HMGB1 biological activity by post-translational modification and redox status [26,39,40]. These modifications can rapidly reverse the role HMGB1 plays in any given setting. Thus, dissecting the role of DAMPs in inflammation is difficult and complex.

It is not yet established whether HMGB1 specifically promotes Th1/Th2 or Th17 responses. One possibility is that HMGB1 can drive multiple pathways, depending on receptor binding, post-translational modifications and/or redox status. There is some evidence that in certain cases HMGB1 can promote Th1 phenotypes in mice [26]. In other cases, HMGB1 has been reported to promote immunosuppression in human cells [35]. Thus, exactly how HMGB1 interfaces with T cell responses and whether different pools of HMGB1 promote different responses has yet to be determined. Some insight to this mechanism may be gleaned from future studies examining the mechanism through which HMGB1 is released by the inflammasome and comparing this with necrotic and apoptotic release mechanisms.

2. Inflammasome

All three of the proteins discussed so far—IL-1β, IL-18 and HMGB1—can be released in a regulated fashion by the cell through a complex termed the inflammasome. The inflammasome is a multi-protein complex that promotes inflammation and immunity. Inflammasome activation is important for the induction of

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