Molecular Immunology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Molecular Immunology

journal homepage: www.elsevier.com/locate/molimm

Transcriptional regulation of inflammasome-associated pattern recognition receptors, and the relevance to disease pathogenesis

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ARTICLE INFO

Article history:
Received 18 June 2016
Received in revised form
23 September 2016
Accepted 26 September 2016
Available online xxx

Keywords:
Inflammasome
Gene expression
Transcriptional regulation
Innate immunity
Inflammation
Cancer

ABSTRACT

Over the last decade it has emerged that inflammasome complexes provide a pivotal platform for the host innate immune system to respond to exogenous infectious microbes (viruses, bacteria, fungi) and non-infectious environmental agents (cigarette smoke, pollution), as well as endogenous "danger" signals. Upon the canonical activation of inflammasomes, a key effector function is to catalyze, via caspase-1, the maturation of the potent pro-inflammatory cytokines interleukin (IL)-1β and IL-18, which, in addition to chronic inflammatory responses have also been intimately linked to the inflammatory form of lytic cell death, pyroptosis. However, recent evidence suggests that inflammasomes exhibit marked pleiotropism beyond their canonical functions, whereby their activation can also influence a large number of cellular responses including proliferation, apoptosis, autophagy and metabolism. It is therefore not surprising that the dysregulated expression and/or activation of inflammasomes is increasingly implicated in numerous disease states, such as chronic auto-inflammatory and autoimmune disorders, metabolic syndrome, neurodegenerative and cardiovascular diseases, as well as cancer. In this review we will highlight recent advancements in our understanding of the transcriptional regulation of genes encoding inflammasome-associated innate immune receptors, and the impact on a variety of cellular responses during disease pathogenesis.

1. Introduction

Innate immune responses elicited within the host against pathogenic microorganisms, environmental factors, and host-derived stress or damage signals depend on the tightly coordinated activation of a series of extracellular and cytosolic receptors called pattern recognition receptors (PRRs), which are widely-expressed in both immune (e.g. macrophage) and non-immune (e.g. epithelial) cells. These PRRs are classified into several large structurally- and functionally-conserved families, including Toll-like receptors (TLRs), absent in melanoma 2 (AIM2)-like receptors (ALRs), and nucleotide-binding oligomerization domain-containing (NOD)-like receptors (NLRs) (Kawai and Akira, 2010; Kersse et al., 2011; Ratsimandresey et al., 2013). Collectively, PRRs trigger inflammatory responses following recognition of diverse ligands comprising invariant products or structures. These ligands are called pathogen-associated molecular patterns (PAMPs) if derived from microbes, or danger-associated molecular patterns (DAMPs), which are endogenous host-derived signals that initiate a "sterile" inflammatory response.

Over the last decade, it has emerged that the activation of specific ALRs and NLRs initiates inflammatory signaling cascades via multiprotein complexes called inflammasomes, which facilitate the maturation and release of the IL-1 cytokine family members, IL-1β and IL-18 (Latz et al., 2013; Stutz et al., 2009). Inflammasomes are critical for driving the recruitment, maturation and activation of immune cells which underpin acute innate immune responses that resolve inflammation and maintain tissue homeostasis, as well as chronic innate immune responses driving uncontrolled inflammation, which can culminate in pyroptotic cell death (Franklin et al., 2014). In recent years, it has become apparent that inflammasome activation can also modulate a wider variety of cellular responses including apoptosis and proliferation of non-immune cells, such as epithelial, endothelial and fibroblast cells (Sagulenko et al., 2013; Yazdi and Drexler, 2015; Wang et al., 2016; Kawaguchi et al., 2011). Collectively, the pleiotropism of inflammasomes is a likely explanation for the diverse pathological consequences of excessive inflammasome activation, which has been linked to chronic

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http://dx.doi.org/10.1016/j.molimm.2016.09.023
0161-5890/

autoimmune, metabolic, cardiovascular, neurodegenerative and inflammatory diseases, and cancer (Strowig et al., 2012). Accordingly, understanding the mechanisms which govern the formation and activation of multi-protein inflammasome complexes has been an intense area of research, and has been extensively reviewed elsewhere (Latz et al., 2013; Strowig et al., 2012; Stutz et al., 2009). By contrast, our understanding of the mechanisms that influence the transcriptional control of inflammasome-related genes is in its relative infancy, which in light of the above-mentioned link between inflammasomes and disease may provide a critical determinant in the net output of inflammasome activity and thereby pathological outcomes. Therefore, this review will summarize current knowledge on the signaling pathways, as well as genetic and epigenetic alterations, which modulate the transcription of inflammasome-related PRR genes, and the potential of these regulatory mechanisms to influence disease pathogenesis.

2. Modes of inflammasome activation, a brief overview

The mechanisms governing the activation of inflammasomes has been extensively reviewed in detail throughout the literature, and below is a brief summary with references to recent reviews comprehensively covering this area. Among members of the NLR family, NLR pyrin domain containing 1 (NLRP1), NLRP3, NLR CARD domain containing 4 (NLRC4), and NLR apoptosis inhibitory protein (NAIP) are best documented for their ability to form the core of distinct cytosolic inflammasomes, with other NLR family members NLRP6, NLRP7 and NLRP12 also being proposed to form specific, albeit less well-characterized inflammasomes (Latz et al., 2013; Lupfer and Kanneganti, 2013; Strowig et al., 2012; Stutz et al., 2009). Collectively, these inflammasomes sense PAMPs and DAMPs of varying diversity, as evidenced by NLRP3-containing inflammasomes that recognize a multitude of structurally-diverse PAMPs and DAMPs (e.g. reactive oxygen species, ATP, crystalline substances such as cholesterol and urea) (Horvath et al., 2011; Strowig et al., 2012). On the other hand, inflammasomes comprising NAIP and NLRC4 are restricted to serving as cytosolic sensors of bacterial flagellin and type III secretion system rod proteins (Zhao and Shao, 2015). In addition to these NLR-based inflammasomes, AIM2 forms an inflammasome following the recognition of double stranded (ds) DNA from numerous bacteria and viruses, as well as host-derived "self-DNA" (Man et al., 2016).

A hallmark of the activation of canonical inflammasomes is the caspase-1-mediated secretion of bioactive IL-1β and IL-18 pro-inflammatory cytokines, and is best exemplified by the activation of NLRP3, which occurs step-wise via both transcriptional and post-transcriptional processes. The first "priming" step involves the transcriptional up-regulation of mRNA for biologically inactive pro-IL-1β and pro-IL-18 precursors, invariably via a PRR-mediated signal, with a prototypical example being lipopolysaccharide (LPS)-induced activation of the TLR4/NF-κB pathway leading to augmented pro-IL-1β mRNA levels (Latz et al., 2013). In the second step, the sensing by each NLR and AIM2 of its specific ligand leads to the recruitment and oligomerization of the key adaptor protein, apoptosis-related speck-like protein containing a CARD (ASC; also known as PYCARD), into large filamentous scaffolds called "specks" (Latz et al., 2013). These ASC speck structures then facilitate the subsequent recruitment and activation of caspase-1, which in turn catalyses the proteolytic cleavage of pro-IL-1β or pro-IL-18 proteins into secreted bioactive cytokines which promote a myriad of inflammatory host responses (Latz et al., 2013).

In addition to canonical inflammasomes comprising NLRP3, ASC and caspase-1, recent studies have identified a non-canonical NLRP3 inflammasome which consists of (mouse) caspase-11 (human caspase-4 and caspase-5 orthologues) and not caspase-1. For instance, in the setting of infection with Gram-negative bacteria, caspase-11 displayed a bimodal role in mediating LPS-induced inflammatory responses by promoting i) pyroptosis and secretion of IL-1α, but not IL-1β, upon TLR4-independent recognition of intracellular LPS, and ii) the assembly of the NLRP3 inflammasome and activation of caspase-1 to process the maturation and secretion of IL-1β or IL-18 from their inactive pro-forms (Kayagaki et al., 2011; Rathinam et al., 2012). The complexities of inflammasome activation are also evidenced by recent studies invoking the existence of additional non-canonical inflammasomes involving the pro-apoptotic caspase-8, whereby in response to Dectin-1 signaling, caspase-8 can be recruited to ASC to facilitate the maturation of IL-β (Gringhuis et al., 2012).

3. Dysregulation of inflammasomes in disease

Excessive activation of inflammasomes has been linked to a wide spectrum of autoimmune and autoinflammatory disorders, reflecting the fact that inflammasomes play a prominent role in the regulation of both adaptive and innate immunity (Broderick et al., 2015). Moreover, in recent years there has been a substantial increase in the spectrum of diseases in which inflammasomes have been implicated, including metabolic syndrome, cardiovascular and neurodegenerative disorders, as well as certain cancers. Considering that the association between inflammasomes and these diseases has been extensively reviewed in detail elsewhere (Broderick et al., 2015; Freeman and Ting, 2016; Henao-Mejia et al., 2014; Zitvogel et al., 2012), below is a brief summary of pertinent clinical data and mouse disease models highlighting the causal relationship between aberrant expression and activation of specific inflammasomes with disease pathogenesis.

3.1. Autoinflammatory and autoimmune disorders

From a historical perspective, the importance of inflammasomes to disease pathogenesis was first reported just over a decade ago, with gain-of-function *NLRP3* gene mutations in patients with a group of rare autoinflammatory diseases, collectively referred to as Cryopyrin-Associated Periodic Syndromes (CAPS), being associated with excessive IL-1β production as a causal factor (Agostini et al., 2004; Hoffman et al., 2001). Although no targeted inflammasome therapies are currently available for clinical evaluation, anti-IL-1 therapies have proved efficacious in the clinic for autoinflammatory disorders characterized by dysregulated IL-1β production driven by the NLRP3 inflammasome (Kuemmerle-Deschner et al., 2013). Further evidence of a disease association between mutations within the *NLRP3* gene and augmented NLRP3 inflammasome activity has arisen from genetically-engineered mouse models bearing knock-in mutations within *Nlrp3* which mimic those observed in human disease; these mice phenocopy many of the hyper-inflammatory pathologies observed in patients with the above-mentioned autoinflammatory disorders (Brydges et al., 2009). In this respect, *Nlrp3*-deficient mouse disease models have suggested NLRP3 also contributes to other chronic autoinflammatory disease, including rheumatoid arthritis (RA) (Vande Walleet al., 2014), an association which is supported by clinical observations that have revealed a disease association between *NLRP3* single nucleotide polymorphisms (SNPs) and augmented mRNA levels in human RA (Mathews et al., 2014).

In addition to autoinflammatory disorders, the NLRP3 inflammasome has been implicated as a casual factor in numerous autoimmune diseases, in particular multiple sclerosis and inflammatory bowel disease (IBD), comprising ulcerative colitis and Crohn's disease. Regarding the latter, *NLRP3* gene polymorphisms which influence both gene expression and inflammasome acti-

Please cite this article in press as: Deswaerte, V., et al., Transcriptional regulation of inflammasome-associated pattern recognition receptors, and the relevance to disease pathogenesis. Mol. Immunol. (2016), http://dx.doi.org/10.1016/j.molimm.2016.09.023