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Review

Inflammasome biology in fibrogenesis ☆

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ABSTRACT

Pathogens and sterile insults both result in an inflammatory response. A significant part of this response is mediated by cytosolic machinery termed as the inflammasome which results in the activation and secretion of the cytokines interleukin-1β (IL-1β) and IL-18. Both of these are known to result in the activation of an acute inflammatory response, resulting in the production of downstream inflammatory cytokines such as tumor necrosis factor (TNF-α), interferon-gamma (IFN-γ), chemotaxis of immune cells, and induction of tissue injury. Surprisingly this very acute inflammatory pathway is also vital for the development of a full fibrogenic response in a number of organs including the lung, liver, and skin. There is evidence for the inflammasome having a direct role on tissue specific matrix producing cells such as the liver stellate cell, and also indirectly through the activation of resident tissue macrophage populations. The inflammasome requires stimulation of two pathways for full activation, and initiating stimuli include Toll-like receptor (TLR) agonists, adenosine triphosphate (ATP), particulates, and oxidative stress. Such a role for an acute inflammatory pathway in fibrosis runs counter to the prevailing association of TGF-β driven anti-inflammatory and pro-fibrotic pathways. This identifies new therapeutic targets which have the potential to simultaneously decrease inflammation, tissue injury and fibrosis. This article is part of a Special Issue entitled: Fibrosis: Translation of basic research to human disease.

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1. Introduction

Fibrogenesis is a common widespread pathophysiological response in many tissues after chronic or repetitive injury including infections, autoimmune reactions, and mechanical injury [1–4]. The initial insults can be amplified by an inflammatory response leading to fibrosis, deposition of extracellular matrix, scar formation, and organ failure [3,5–7]. Innate immune cells residing in tissues recognize pathogen invasion with intracellular or surface-expressed pattern recognition receptors (PRRs) by detecting pathogen-associated molecular patterns (PAMPs) [8]. PPRs can also be activated by damage-associated molecular patterns (DAMPs) from injured cells leading to sterile inflammation to distinguish from that induced by pathogens [9]. Inflammasomes are a group of protein complexes that recognize a diverse set of inflammation-inducing stimuli that include PAMPs and DAMPs and that control activation of the proteolytic enzyme caspase-1, which in turn regulates maturation of the pro-inflammatory cytokines interleukin-1β (IL-1β) and IL-18 [10,11]. Inflammasomes have been found to regulate important aspects of inflammation and tissue repair such as fibrogenesis, a consequence of inflammatory response [12]. Recent studies have characterized distinct molecular activation mechanisms for several sensor proteins and have described the important implication of those components in immune-mediated pathogenesis in humans. We review recent research progress, discuss the different aspects that have been proposed for inflammasome involvement in fibrogenesis during disease development, and highlight the challenges and future directions for this field.

2. Sterile inflammation

Inflammation derived by the innate immune response has evolved to efficiently combat infection with pathogenic microorganisms and is critical to host defense. However, such innate mechanisms can also be activated as result of a sterile cell death or injury in the absence of any microorganism, and has been termed 'sterile inflammation' [13]. Similar to microbial-induced inflammation, sterile inflammation is characterized by the accumulation of neutrophils and macrophages, and the production of pro-inflammatory cytokines and chemokines, especially tumor necrosis factor (TNF) and interleukin 1-β (IL-1β), as well as reactive oxygen species [13,14]. Sterile inflammation can be induced by many DAMPs including adenosine triphosphate (ATP) and uric acid, which have the ability to activate inflammation in the non-infectious immune response. A large and varied number of DAMPs applied to self molecules have been identified as endogenous factors that can be released or generated into the extracellular environment by dying cells or secondarily abnormal metabolism, and trigger sterile inflammation

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under conditions of cellular stress or injury [15]. The actual repertoire of DAMPs in damaged tissues can vary greatly depending on the type of cell and injured tissue, as illustrated by DAMPs released from parenchymal cells after drug-induced hepatocyte cell death [16]. Prototypical DAMPs derived from necrotic cells include intracellular proteins, such as the chromatin associated protein high-mobility group box 1 (HMGB1) [17], heat shock proteins (HSPs) [18,19], and proteins derived from the extracellular matrix that are generated following tissue injury, such as hyaluronan, heparin sulfate and biglycan. These are generated as a result of proteolysis by enzymes released from dying cells or by proteases activated to promote tissue repair and remodeling [20,21]. Non-protein DAMPs are released or generated during cell death or purine metabolites, such as ATP [22] and uric acid [23]. Recently, mitochondria have emerged as organelles that provide a rich source of DAMPs including mitochondrial DNA, formyl peptides, cytochrome C and ATP. Such a concentration of DAMPs makes mitochondria very potent stimulators of inflammation [24,25]. The variety of DAMP components derived from mitochondria further increases their ability to induce inflammation as they can provide the full range of signals required to initiate sterile inflammation. In addition to those typical DAMP molecules, some biologically active pro-inflammatory cytokines and chemokines, such as IL-1α [26] and IL-33 [27] can be released by necrotic cells, serve a similar function as conventional DAMPs. The importance of cell death in relation to the production of DAMPs and sterile inflammation is that it provides a pathway of regulated pro-inflammatory type of cell death. However, HMGB1 can be secreted by activated macrophages in response to LPS, TNF and TGF-β [28]. This confirms the functional pro-inflammatory actions of HMGB1 independent of cell death.

A wide range of in vivo and external particulates have been found to trigger sterile inflammation, in some cases those particulates elicited response associates with prominent fibrogenesis. These particles include inorganic (silica dioxide) [29], organic (cholesterol), crystalline (uric acid crystals), or amorphous such as alum [30,31]. Initially it seems unlikely that significant amounts of organic particulates are present in vivo, however recent examination of liver tissues from humans and mice have shown that with fat-induced inflammation, but not simple steatosis, cholesterol crystals are present inside hepatocytes and come into contact with Kupffer cells [32]. When other non-organic particulates such as talc in intravenous drug users enter organs such as the liver there is also a strong fibrotic response [33]. The further results from our research group have shown that implantation of biomaterials and devices into soft tissues leads to the development of a sterile foreign body response (FBR), which can interfere with implant function and eventually lead to failure [34]. Most of these parts for a number of these particles the inflammatory response results in tissue damage and its attendant fibrogenesis can lead to loss of function. Approximately 20 DAMPs have been identified and it is likely that many others are present in vivo.

3. Components of inflammasomes

Until recently, much more was known about how innate immunity is activated by pathogens than by sterile particles and dead cells. The innate immune system possesses multiple families of germ-line encoded PRRs. These PRRs include the Toll-like receptors (TLRs), NOD-like receptors (NLRs), C-type lectin receptors (CLRs), and several other receptors [35–37], all of which contribute to immune activation in response to diverse stimuli. These include infectious and noninfectious materials that can cause tissue damage, and endogenous molecules that are released during cellular injury. Activation of these receptors ultimately leads to the production of cytokines that drive the inflammatory response. DAMPs are the best characterized candidates that know to activate PRRs and trigger sterile inflammation. Like all the other innate immune receptor molecules, the NLR proteins are involved in sensing the presence of pathogens via PAMPs; however, they also can detect endogenous danger or stress signals via DAMPs. A subset of NLRs forms a complex with ASC (apoptosis-associated speck-like protein containing a CARD) to activate caspase-1 and induce maturation and secretion of important pro-inflammatory cytokines such as interleukin-1β (IL-1β) and IL-18, whose potent pro-inflammatory activities direct host responses to infection and injury. Those complexes firstly were termed as inflammasome by the Tschopp research group [38]. The diverse functions of inflammasomes in antimicrobial responses, as well as in multifaceted diseases such as acute liver injury and metabolic syndrome, have become evident. Importantly, mutations in components of inflammasome complexes have been associated with a propensity for the development of several immune-mediated diseases in humans.

The inflammasome is composed of a sensory molecule that is a member of the family of nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), which can be divided into three subfamilies: NLRP, NOD and ICE-protease-activating factor (IPAF)/neuronal apoptosis inhibitory protein (NAIP) based on their molecular structure and function [10]. These sensory molecules interact with the intermediary adaptor molecule ASC, which in turn can activate cellular proteases. The sensory molecules are cytoplasmic pattern-recognition receptors that recognize a range of molecules ranging from PAMPs to danger signals, such as uric acid and a variety of others. The human NLR family consists of 22 members that can be sub-grouped based on their N-terminal domain which include caspase-recruitment domain (CARD), pyrin domain (PYD), and baculovirus IAP repeat domain (BIR).

Upon activation, NLR family members form the multiprotein complexes called the inflammasome. In addition, the cytosolic AIM2 (absent in melanoma 2) molecule is also capable of forming an inflammasome complex. The inflammasome serves as a platform for activation of the cysteine protease caspase-1 which cleaves the pro-forms of the cytokines IL-1β and IL-18 to their active and secreted forms. Caspase-1 may also possess additional functions including regulation of metabolism [39] and unconventional protein secretion [40]. The NLRP3 inflammasome has been associated with a wide range of diseases including infectious, auto-inflammatory, and autoimmune disorders. Bacterial, fungal, viral, and protozoan parasitic pathogens have all been demonstrated to activate the NLRP3 inflammasome [41,42]. NLRP3 is likely responding to the cellular stress induced by the infectious agents and DAMPs and mitochondria are likely central to co-ordinating this process.

IL-1β is activated by caspase-1 and is a proximal pro-inflammatory cytokine that broadly affects inflammatory processes. IL-1β is synthesized as a pro-protein without a typical signal sequence that would allow its secretion, and instead its activation and cellular release are controlled by caspase-1 [43]. Caspase-1 is also responsible for the secretion of IL-1α and fibroblast growth factor-2 through an unconventional protein secretion pathway [40]. Caspase-1 is constitutively expressed as pro-caspase-1, but it remains inactive in the cytoplasm until inflammatory effector cells such as monocytes and macrophages receive appropriate stimuli. Known activators are changes in the intracellular ionic environment and bacterial products such as lipopolysaccharide (LPS) and peptidoglycan [44,45]. Inflammasome machinery recruits pro-caspase-1 either directly through homotypic binding of CARD or indirectly through PYD of ASC protein.

4. Regulation of inflammasome activity

In the current model of inflammasome activation there are two distinct signals. The first signal can be triggered by various PAMPs following TLR activation signal as well as IL-1R signaling, and the activation of tumor necrosis factor receptor (TNF-R) (Fig. 1). This priming signal leads to transcription activation of the genes encoding pro-IL-1β, pro-IL-18 and NLRP3 [46,47]. The second signal is provided by various inflammasome ligands through cytosolic NLR inflammasome activation leading the cleavage of pro-IL-1β and pro-IL-18 into the active forms [48,49]. In the second signal model, after phagocytosis of large crystals such as monosodium urate (MSU), silica, asbestos and aluminum salts,