Joint Bone Spine 81 (2014) 398–402

Available online at
SciVerse ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Review

The concept of the inflammasome and its rheumatologic implications

Alexander So*, Nathalie Busso

Service de rhumatologie, université de Lausanne, CHU Vaudois, avenue Pierre-Decker 4, 1011 Lausanne, Suisse

ARTICLE INFO

Article history:
Accepted 15 February 2014
Available online 2 April 2014

Keywords:
IL1β
Inflammasome
Auto-inflammatory disorders
Gout

ABSTRACT

The inflammasome is a proteolytic complex that regulates IL1β and IL-18 secretion in macrophages and dendritic cells. Its plays a vital role in the control of the inflammatory and cellular responses to infectious and danger signals and is an essential part of the innate immune system. Four different inflammasomes have been identified so far, and the NLRP3-inflammasome has been the best-studied in relation to human disease. Activation of the NLRP3-inflammasome by microcrystals, such as monosodium urate (MSU) and basic calcium phosphate (BCP) crystals, leads to IL1β release, which in turn triggers local inflammation. Dysfunction of the NLRP3-inflammasome due to mutations of the NLRP3 gene is the cause of the auto-inflammatory syndrome CAPS. The symptoms and signs of inflammation in both conditions respond to IL1 blockade. IL1 inhibitors have also been used successfully in other idiopathic inflammatory diseases, suggesting that dysregulated inflammasome activity contributes to the pathogenesis of multiple diseases, but the precise underlying mechanisms remain to be identified.

1. Introduction

The inflammasome was the name first given by Jürg Tschopp and his colleagues to an intracellular complex of proteins that activated caspases and triggered the processing and secretion of IL-1β [1]. This complex, which currently has 4 distinct variants, together with the Toll-like receptor (TLR) and Rig-like helicases (RLH) families of receptors, acts as an alarm system to alert the cell to danger signals from exogenous pathogens, toxins, cellular stress or cellular damage. Multiple downstream effects of inflammasome activation have been described, including cellular activation, release of pro-inflammatory cytokines and programmed cell death. In human disease, the inflammasome has been linked primarily to auto-inflammatory diseases, but it has also been implicated in diverse chronic disorders such as atherosclerosis and diabetes.

Four types of inflammasome have been identified: the NLRP1 (NOD-, LRR- and pyrin domain-containing 1), NLRP3, NLRC4 (NOD-, LRR- and CARD-containing 4) and AIM2 (absent in melanoma 2) inflammasomes (Table 1). Although the composition of each inflammasome is unique, they share common features: one of the components is a member of the NLR (NOD-like receptor) family of proteins and their are all able to recruit and activate caspases (principally caspase-1 and caspase-12). These active caspases then cleave a range of cytoplasmic targets, including pro-IL-1β and pro-IL-18 to form mature IL-1β and IL-18, which are secreted from the cell. The best-studied inflammasome is probably the NLRP3-inflammasome, which is triggered by a large range of substances (see Table 1), but the scope of this review is focused on rheumatic diseases, where knowledge of the underlying mechanisms as well as the effects of treatment is best documented.

2. Inflammasome activation occurs through multiple pathways

The activity of the inflammasome is enhanced during inflammation. Part of this is accounted for by increased transcription of the components such as NLRP (for example after stimulation by TLRs), but it is also be due to the action of co-factors that alter the threshold of inflammasome formation and activity. A large number of different substances can activate the NLRP3-inflammasome (listed in Table 1). Two major classes of inflammasome activators emerge from the available data: one that is grouped as particulate activators, which include microparticles and crystals, and the other group consists of soluble ligands, usually of bacterial origin. Their very different molecular compositions suggest that there are common intermediate pathways that are shared by the different activators. Table 2 summarizes the different mechanisms of inflammasome activation that have been identified so far, some of which are the results of changes in cellular composition following cell stress, and others represent novel proteins that interact and influence the assembly or activation of the inflammasome complex.

Research has revealed several mediators that seem to have crucial roles in specific activation pathways, but so far only one – RNA-activated protein kinase (PKR; also known as EIF2AK2) – has been identified as a common intermediate in all mechanisms of inflammasome activation.

* Corresponding author.
E-mail address: alexanderkai-lik.so@chuv.ch (A. So).

1297-319X/$ – see front matter © 2014 Société française de rhumatologie. Published by Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.jbspin.2014.02.009

Table 1
Inflammasomes: composition and activators.

Inflammasome	Synonyms	Components	Processed cytokine(s)	Cellular effect	Activators
NLRP1	NALP1	ASC, CARD8, caspase-1, caspase-5	IL-1β	Pyroptosis	MDP, anthrax lethal toxin
NLRP3	NALP3, cryopyrin	ASC, caspase-1	IL-1β, IL-18	Apoptosis, pyroptosis	Microcrystals (MSU, CPPD, BCP, alum, oxalate and cholesterol), nanoparticles, ATP, oxidized DNA, RNA, bacterial toxins, *Salmonella typhimurium*
AIM2	–	ASC, caspase-1, caspase-3, caspase-8	IL-1β	Apoptosis	dsDNA, *Mycobacterium tuberculosis*, *Francisella tularensis*
NLRC4	IPAF	NAIP2, NAIP5, caspase-1	IL-1β, IL-18	Pyroptosis	*Pseudomonas* spp., *Salmonella* spp., *Legionella* spp., *Yersinia* spp., flagellin, PrgJ

AIM2: absent in melanoma 2; BCP: basic calcium phosphate; CARD8: caspase-recruitment domain-containing protein 8; CPPD: calcium pyrophosphate dihydrate; dsDNA: double-stranded DNA; IL: interleukin; MDP: muramyl dipeptide; MSU: monosodium urate; NAIP: neuronal apoptosis inhibitory protein; NLRC4NOD-, LRR- and CARD-containing 4; NLRPNOD-, LRR- and pyrin domain-containing.

Table 2
Mechanisms of inflammasome activation.

Pathway	Intermediate or mechanism	Examples
Oxidative stress	ROS	Implicated in infection-induced and microcrystal-induced inflammasome activation
	TXNIP	Implicated in glucose-dependent inflammasome activation
Cationic shift	K^+ efflux	Occurs through P2X7 or pannexin-1
	Ca^{2+} mobilization	Released from the endoplasmic reticulum on triggering of calcium sensing receptor, via PLC activation
Protease activity	Release of cathepsin B from phagolysosomes	Mediates crystal-induced inflammasome activation
Mitochondrial stress	MAVS	Mitochondrial accessory protein essential in non-crystalline inflammasome activation
	Oxidized mtDNA	Secondary to mitochondrial ROS generation
Other pathways	PKR	Implicated in all forms of inflammasome activation
	GBP5	Required in infection-mediated NLRP3 activation

3. Inflammasome and crystal-induced diseases

Pathogenic microcrystals in rheumatic and non-rheumatic diseases include monosodium urate (MSU), calcium pyrophosphate dihydrate (CPPD), basic calcium phosphate (BCP), oxalate and cholesterol. These crystals differ in physical and chemical properties, but because of their crystal structure, they have a number of common biological effects on cells that they come into contact with. When macrophages encounter crystals *in vitro*, membrane interactions initiate phagocytosis, leading to activation of the NLRP3-inflammasome and IL1β processing and release. This occurs only in "primed" macrophages, that is macrophages that have received a prior signal to initiate the transcription of IL1. This priming signal include long-chain fatty acids and other ligands that can bind to TLR2 on the surface of macrophages. Without this priming, macrophages do not produce significant amounts of IL1β. In contrast, synovial fibroblasts and chondrocytes do not release IL1β when cultured with crystals, even after priming (unpublished data).

In vivo, the need for the inflammasome in IL1β production is not so clear-cut. In animal models of crystal-induced inflammation, IL1β release occurs even in the absence of components of the inflammasome. However, the inflammatory phenotype (accumulation of neutrophils) is dependent on IL1, as it is completely blocked when the IL1R is inhibited. Two mechanisms may account for these observations: firstly that there is an inflammasome-independent mechanism for the release of IL1β; and secondly that besides IL1β, IL1α that is not inflammasome dependent in its secretion, can also participate in the inflammatory process [2].

Gout is characterized by recurrent episodes of acute inflammation triggered by tissue deposits of MSU crystals. The role of IL1 in this disease is exemplified by the experimental data described above, and by the effects of IL1 inhibition in gout. In uncontrolled studies, anakinra was found to be extremely effective in controlling the signs and symptoms of acute gout in patients who had contraindications to, or were unresponsive to NSAIDs and colchicine [3–5]. Randomized controlled trials with two different IL1 inhibitors, canakinumab (anti-IL1β monoclonal antibody) and rilonacept (IL-1 Trap, capable of binding IL1α and β) confirmed the efficacy of IL-1 inhibition in different settings of gouty arthritis. These included the prevention of acute flares in patients who were started on urate lowering therapy, and in patients who could not tolerate and had contraindications to colchicine or NSAIDs as treatment of an acute attack. [6–9]. All the results indicate that IL-1 inhibition is effective during acute gout and in the prevention of a gout flare (see below). Canakinumab has now been approved by the EMEA as a treatment of acute gout in patients who are either intolerant or have contraindications to colchicine, NSAIDs as well as corticosteroid therapy. Although only a small proportion of the gouty population fulfils all these criteria, IL1 inhibition can be helpful in acute gouty patients who have multiple medical co-morbidities (renal and cardiac insufficiencies) and who have limited treatment options.

In the case of other forms of microcrystal-induced arthritis, anecdotal data demonstrate that IL-1 inhibition is effective in CPPD-induced arthritis [10–12] and in BCP-induced calcific tendinitis [13]. No controlled studies have been performed to date in these two conditions.

Why is gout only inflammatory intermittently, even though MSU crystals are present constantly? One explanation is that natural anti-inflammatory mechanisms – such as the secretion of transforming growth factor-β by macrophages – dampen the inflammatory response. Another potential explanation is that for full-blown inflammation to develop in the clinical setting a priming trigger is needed (see above). Indeed, in an animal model of gouty arthritis, MSU crystals injected into the joint alone were insufficient to induce inflammation. By contrast, robust arthritis was observed when these crystals were co-injected with long-chain fatty acids that can activate cells via TLR2 signalling ten [14]. We still do not have clear evidence that specific dietary or environmental triggers are responsible for a gouty attack, but epidemiological data suggest