BJA

British Journal of Anaesthesia, 117 (6): 693–707 (2016)

doi: 10.1093/bja/aew376
Review Article

REVIEW ARTICLE

The inflammasome as a target for pain therapy

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Abstract

The interleukin-1 family of cytokines are potent inducers of inflammation and pain. Proteolytic activation of this family of cytokines is under the control of several innate immune receptors that coordinate to form large multiprotein signalling platforms, termed inflammasomes. Recent evidence suggests that a wide range of inflammatory diseases, cancers, and metabolic and autoimmune disorders, in which pain is a common complaint, may be coordinated by inflammasomes. Activation of inflammasomes results in cleavage of caspase-1, which subsequently induces downstream initiation of several potent pro-inflammatory cascades. Therefore, it has been proposed that targeting inflammasome activity may be a novel and effective therapeutic strategy for these pain-related diseases. The purpose of this narrative review article is to provide the reader with an overview of the activation and regulation of inflammasomes and to investigate the potential therapeutic role of inflammasome inhibition in the treatment of diseases characterized by pain, including the following: complex regional pain syndrome, gout, rheumatoid arthritis, inflammatory pain, neuropathic pain, chronic prostatitis, chronic pelvic pain syndrome, and fibromyalgia. We conclude that the role of the inflammasome in pain-associated diseases is likely to be inflammasome subtype and disease specific. The currently available evidence suggests that disease-specific targeting of the assembly and activity of the inflammasome complex may be a novel therapeutic opportunity for the treatment of refractory pain in many settings.

Key words: caspase 1; inflammasomes; inflammation; interleukins; NOD-like receptor; pain

The interleukin-1 (IL-1) family of cytokines is composed of 11 isoforms, all of which share the characteristic of their ability to induce inflammation. The principal species, IL-1β, possesses strong pro-inflammatory effects on a variety of cells, and its aberrant production contributes to acute and chronic inflammation and pain.[1 2] Notably, increased IL-1 activity is associated with autoimmune disorders, such as rheumatoid arthritis (RA), inflammatory bowel disease, multiple sclerosis (MS), and Alzheimer's disease (AD),[1–4] which are all conditions in which pain is a common complaint. The pain-inducing mechanisms of IL-1β include the direct activation of neuronal activity in the peripheral and central nervous system, and IL-1β acts as a mediator that stimulates the production of additional algogenic substances.[2 5–8] Blocking the IL-1β signalling pathways has proved to be highly effective in reducing inflammatory pain sensitization in animal models[2 6 8–10] and patients.[2 11 12] However, the mechanisms underlying the aberrant upregulation of IL-1β were largely unknown before the recent discovery of the inflammasome by Martinon and colleagues.[13]

Inflammasomes are multiprotein complexes that coordinate to activate caspase-1, an IL-1-converting enzyme.[13–16] Cleavage of the inactive IL-1β and IL-18 precursors (pro-IL-1β and pro-IL-18) with caspase-1 is a prerequisite for activation. Like IL-1β, caspase-1 is synthesized as an inactive 45 kDa enzyme,

pro-caspase-1, which also requires inflammasome activity for cleavage. Given that IL-1β plays a well-established role in inflammation and pain and that inflammasomes are able to sense a wide range of danger signals, such as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) to control IL-1 production,[17] inflammasomes may play a central role in supporting pain in a diverse range of conditions. Predictably, this discovery has promoted research investigating the potential targeting of inflammasomes both to control inflammation and to reduce the associated pain. This type of approach may be particularly important in diseases where inflammasome dysfunction has been shown to play a central role.[1 18–20]

In this review, we present a narrative overview of the current understanding of inflammasome activation and regulation. We then address the question of whether inflammasomes may be a potential target for pain therapy in pain-associated disease by reviewing current literature on the role of inflammasomes in various pain-related disease states.

This was accomplished by an electronic database search of PubMed and Google Scholar with several key terms. These terms included the following: 'inflammasome, inflammation, NLRP, NALP, cytokines, IL-1, IL-18, immune, purinergic receptors, immunoglobulin, pain, hyperalgesia, inflammatory pain, neuropathic pain, complex regional pain syndrome, gout, migraine, chronic prostatitis, chronic pelvic pain syndrome, fibromyalgia, autoimmune disorder, arthritis, multiple sclerosis, Alzheimer's disease, cancer, pathogen associated molecular patterns, damage associated molecular patterns, and toll like receptors'. In addition, articles relevant to our discussion were retrieved from the reference list of other online articles on each subtopic. Articles in a language other than English and conference abstracts were excluded from further consideration. In the end, 150 articles closely related to the aims set forth for this review were selected and used.

The following questions were addressed in constructing the review. What is our current understanding of inflammasome activation and regulation? What roles does the inflammasome play in pain-associated diseases? Are inflammasomes potential targets for pain-associated diseases?

Inflammasome composition and subtypes

A summary of inflammasome structure and activation is presented in Fig. 1 and Table 1.//// The multiprotein inflammasome complex contains a nucleotide-binding oligomerization domain (NOD)-like receptor (NLR), an adaptor protein apoptosis-associated speck-like protein (ASC, which contains a caspase-activating recruitment domain), and pro-caspase-1, pro-caspase 5, or both. NLRs contain the following three domains: a nucleotide-binding domain (NBD), which mediates adenosine triphosphate (ATP)-dependent self-oligomerization;[38] a

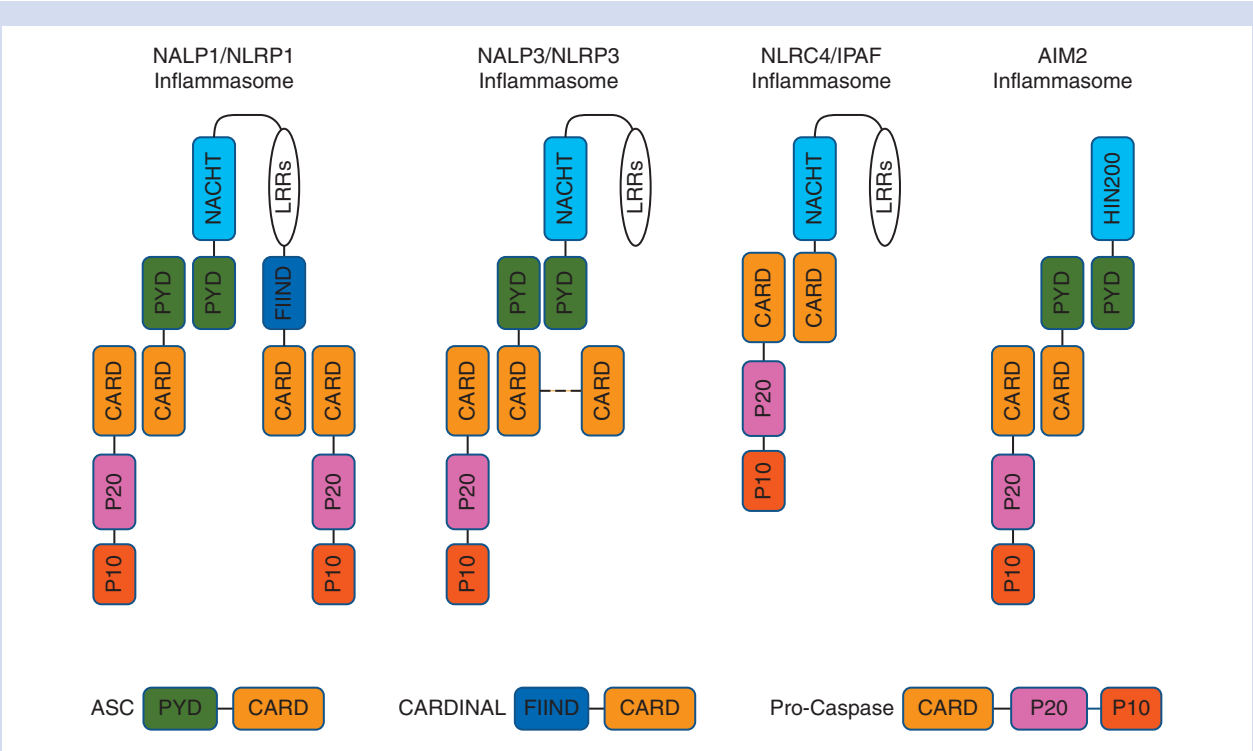

Fig 1 Schematic diagram illustrating the composition of inflammasomes. The activation and formation of inflammasome complexes is mediated through several protein domains. NLRs are characterized by the combined presence of a NACHT domain and LRRs. Most NLRs also contain either a CARD or a PYD motif in their amino terminus. AIM2 is composed of an amino-terminal PYD and a carboxy-terminal DNA-binding HIN200 domain. Murine NALP1 lacks the amino-terminal PYD motif found in human NALP1 and is autocatalytically cleaved in its central FII domain. CARD, caspase activation and recruitment domain (orange rectangles); Caspase domain, p20 and p10 as the large and small subunits, respectively (pink and red rounded rectangles); FIIND, function-to-find domain (blue rectangles), which is involved in NALP1 inflammasome activation through auto-proteolysis; HIN: haematopoietic, interferon-inducible, nuclear localization domain (light blue rounded rectangles); LRRs, leucine-rich repeats (white elongated ovals); NACHT, nucleotide-binding and oligomerization domain (light blue and grey rounded rectangles); NLR, NOD-like receptor; PYD, pyrin domain (green rectangles). NLRP1/NALP1, leucine-rich repeat and pyrin domain containing protein 1; NLRP3/ NALP3, leucine-rich repeat and pyrin domain containing protein 3; IPAF/NLRC4, NLR family CARD domain-containing protein 4; ATP, adenosine triphosphate; AIM2, absent in melanoma 2; ASC, apoptosis-associated speck-like protein; CARDINAL, the card containing protein; dsDNA, double-stranded DNA.