Review

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Inflammasomes in liver diseases

Gyongyi Szabo*, Timea Csak

Department of Medicine, University of Massachusetts Medical School, Worcester, USA

Summary

Inflammation is a common element in the pathogenesis of most chronic liver diseases that lead to fibrosis and cirrhosis. Inflammation is characterized by activation of innate immune cells and production of pro-inflammatory cytokines IL-1α, IL-1β, and TNFα. Inflammasomes are intracellular multiprotein complexes expressed in both parenchymal and non-parenchymal cells of the liver that in response to cellular danger signals activate caspase-1, and release IL-1β and IL-18. The importance of inflammasome activation in various forms of liver diseases in relation to liver damage, steatosis, inflammation and fibrosis is discussed in this review.

Inflammasomes and their signal transduction pathways

The term "inflammasome", introduced by Tschopp and colleagues [1] refers to large multiprotein complexes that sense intracellular danger signals via NOD-like receptors (NLR) [2].

NOD-like receptors, members of the pattern recognition receptor family, contain a C-terminal leucin-rich-repeat (LRR) domain that plays a role in the recognition of ligands, a central NACHT domain that is responsible for the oligomerization and dNTPase activity, and an N-terminal CARD, pyrin (PYD), BIR (baculoviral inhibitory repeat), or acidic transactivation domain. Based on the NACHT domain, three subfamilies of proteins are defined: (a) NODs, (NOD1–5, CIITA), (b) NLRPs or NALPs (NLRP/NALP 1–14), and (c) IPAF (IPAF, NAIP) subfamily [2] (summarized in Fig. 1). Other classifications, based on the N-terminal effector domain, are also known [3]. Several, but not all, NLRs play a role in the formation of inflammasomes. With the exception of AIM2, which is a member of the HIN-200 family, the nomenclature of inflammasomes is based on the NOD-like receptor (NLR).

Key Points 1

Nod like receptors (NLRs) contain a C-terminal leucin-rich-repeat (LRR) domain that plays a role in the recognition of ligands, a central NACHT domain that is responsible for the oligomerization and dNTPase activity, and an N-terminal CARD, pyrin (PYD), BIR (baculoviral inhibitory repeat), or acidic transactivation domain. NLRs have been grouped into subfamilies by either the NACHT domain or the N-terminal domain. Several, but not all, NLRs play a role in the formation of a multiprotein complex called the inflammasome. In addition, non-NLR proteins, such as AIM2 can also form a complex with caspase-1

The sensor, NLR, forms a complex with the effector molecule, pro-caspase-1, with or without the contribution of an adapter molecule, such as the apoptosis-associated speck like CARD-domain containing protein (ASC) [1–4]. Inflammasome activation leads to auto-activation of the 45 kDa inactive pro-caspase-1 precursor into p20 and p10 subunits that form the active caspase-1 [1–4], resulting in the cleavage of pro-IL-1β and pro-IL-18 into mature forms, and inactivation of IL-33 [1–5]. IL-1β is a pro-inflammatory cytokine, a central regulator of inflammation that binds to the IL-1 receptor (IL-1R) to exert its broad biological effects. IL-1R also recognizes IL-1α and binds IL-1R antagonist (IL-1Ra), the latter inhibiting IL-1R activation [6]. IL-18 activates natural killer (NK) cells to produce IFNγ [6], while IL-33 is a chromatin-associated cytokine of the IL-1 family that drives Th2 responses [4,6]. The full-length active IL-33 is cleaved and inactivated by caspase-1 [5].

Inflammasome activation is thought to be a two-step process in which signal 1 (mostly from TLR activation) upregulates inflammasome expression and signal 2 triggers functional inflammasome activation by an inflammasome ligand [2,4]. A recent publication suggests that the priming step is required only for activation of NLRP3 and not other inflammasomes such as

Keywords: Inflammasomes; Interleukin-1ß; Caspase-1; Drug induced liver injury; Ischaemiareperfusion; Endotoxin; Steatohepatitis; Viral hepatitis; Fibrosis.
Received 4 November 2011; received in revised form 6 March 2012; accepted 8 March 2012

* Corresponding author. Address: University of Massachusetts Medical School, Department of Medicine, LRB215, 364 Plantation Street, Worcester, MA 01605, USA. Tel.: +1 508 856 5275; fax: +1 508 856 4770.
E-mail address: gyongyi.szabo@umassmed.edu (G. Szabo).

Abbreviations: NLR, NOD-like receptor; ASC, apoptosis-associated speck like CARD-domain containing protein; IL, interleukin; IL-1R, interleukin-1 receptor; IL-1Ra, interleukin-1 receptor antagonist; NK, natural killer; IFN, interferon; TLR, toll-like receptor; PAMP, pathogen associated molecular pattern; DAMP, damage associated molecular pattern; NALP1, NACHT, LRR, and PYD domains-containing protein 1; NALP3, NACHT, LRR, and PYD domains-containing protein 3/cryoporin; NLRC4, NLR-family CARD domain containing protein 4; AIM2, absent in melanoma 2; MDP, muramyl dipeptide; NFκB, Nuclear factor kB; MSU, monosodium urate; ROS, reactive oxygen species; NADPH, nicotinamide adenine dinucleotide phosphate oxidase; ATP, adenosine triphosphate; TXNIP, thioredoxin-interacting protein; RIG-I, retinoic acid-inducible gene-I; APAP, N-acetyl-p-aminophenol; I/R, ischaemia-reperfusion; LPS, lipopolysaccharide; ASH, alcoholic steatohepatitis; NASH, nonalcoholic steatohepatitis; MCD, methionine-choline deficient; HFD, high fat diet; CDAA, choline deficient amino acid defined; TNFα, tumor necrosis factor α; MyD88, myeloid differentiation factor 88; CCl4, carbon tetrachloride; HCV, hepatitis C virus; HBV, hepatitis B virus.

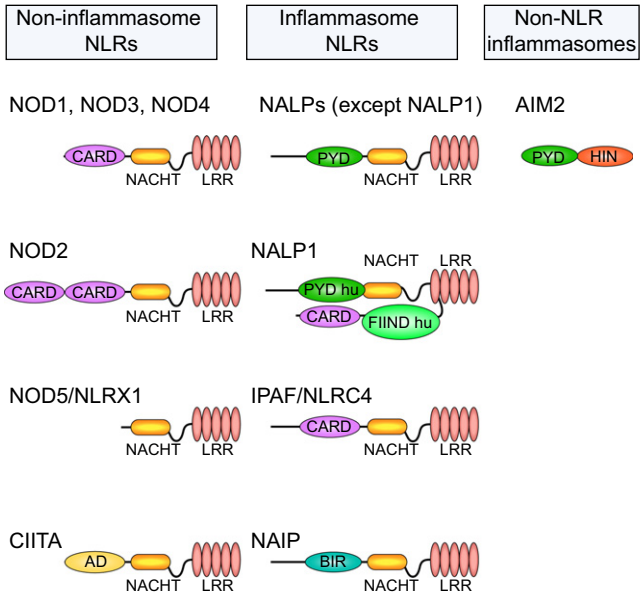

Fig. 1. Structure of inflammasome and non-inflammasome NLRs and non-NLR inflammasomes.

NLRC4 or AIM2 [7]. Inflammasome ligands include both pathogen-associated (PAMPs) and endogenous danger molecules (DAMPs) (summerized in Table 1) [1–4]. To date, four main prototypes of inflammasomes have been characterized: NLRP1 (NALP1); NLRP3 (NALP3, cryporin); NLRC4 (IPAF) and AIM2 [2,4]. They have different ligand recognition sites and utilization of adapter molecules but all culminate in caspase-1 activation.

NLRP1 inflammasome

NLRP1 (NACHT, LRR, and PYD domains-containing protein 1), the first inflammasome described, can directly interact with caspase-1 through its C-terminal CARD domain, and in humans, the presence of ASC enhances the activity of the complex [34]. Murine NLRP1 is unable to bind to ASC because it lacks a functional PYD domain [34]. Multiple alternatively spliced transcript variants of human NLRP1 exist [35].

NLRP1 is activated by the muramyl dipeptide (MDP) and the *Bacillus anthracis* lethal toxin [8–11]. An interaction was reported between NLRP1 and another NLR protein, NOD2, and Hsu *et al.* found that NLRP1 and NOD2 were both required for MDP or *B. anthracis* toxin-induced IL-1β secretion [11]. Potassium efflux plays a role in NLRP1 inflammasome activation [9] and NLRP1 can localize into the nucleus, and this feature is unique in

Review

Table 1. Known activators of inflammasome NLRs.

Inflammasome	Activator
NLRP1 (NALP1)	*Bacillus anthracis* lethal toxin [8-11] MDP [10,11]
NLRP3 (NALP3, cryoporin)	**Large particles via phagocytosis** Monosodium urate crystals (MSU) [12] CPPD (calcium pyrophosphate dehydrate) [12] Alum [13] Silica [14] Asbestos [15] Amyloid beta [16] Hyaluronan [17] Hemozoin [18] Vaccine adjuvants (poly lactide-co-glycolide and polystyrene microparticles) [19] Cholesterol crystals [20]
	Bacterial toxins (pore-forming) *Listeria monocytogene*s Lysteriolysin O [21,22] *Staphylococcus aureu*s alpha-toxin [21-23] *Aeromonas hydrophila* aerolysin [21,22] Streptolysin [24] Nigericin [21] Maitoxin (Dinoflagellates) [22]
	Ion channels and activators ATP(P2X7) [21] Influenza virus M2 channel protein [25]
	PAMPs (only if transferred to the cytoplasm by e.g. Streptolysin O pore-forming toxin) LPS, lipid A, PGN, MDP, LTA, Pam3, ssRNA, dsRNA, CpG DNA [26,27]
NLRC4 (IPAF)	**Gram - negative bacteria (flagellin-dependent and independent)** *Salmonella typhymurium* [28] *Shigella flexneri* [28,29] *Legionella pneumophila* [30] *Pseudomonas aeruginosa* [28]
AIM2	**dsDNA** bacterial [31,32] viral [31,32] mitochondrial [33] host [31]