Institut Pasteur
Microbes and Infection 15 (2013) 630–639
www.elsevier.com/locate/micinf

Review

NLRP7 and related inflammasome activating pattern recognition receptors and their function in host defense and disease

Alexander D. Radian [a,b], Lucia de Almeida [a], Andrea Dorfleutner [a], Christian Stehlik [a,c,*]

[a] Division of Rheumatology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA
[b] Driskill Graduate Program in Life Sciences (DGP), Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA
[c] Robert H. Lurie Comprehensive Cancer Center, Interdepartmental Immunobiology Center and Skin Disease Research Center, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA

Received 7 January 2013; accepted 9 April 2013
Available online 22 April 2013

Abstract

Host defense requires the maturation and release of the pro-inflammatory cytokines interleukin (IL)-1β and IL-18 and the induction of pyroptotic cell death, which depends on the activation of inflammatory Caspases within inflammasomes by innate immune cells. Several cytosolic pattern recognition receptors (PRRs) have been implicated in this process in response to infectious and sterile agonists. Here we summarize the current knowledge on inflammasome-organizing PRRs, emphasizing the recently described NLRP7, and their implications in human disease.

Keywords: Inflammasome; Pattern recognition receptor; Nod-like receptor; AIM2-like receptor; Inflammation; Hydatidiform mole

1. Introduction

To maintain tissue homeostasis, a strong defense against pathogenic microorganisms as well as the restriction of commensal bacteria is crucial. Pattern recognition receptors (PRRs) are germline-encoded "sensors" of the innate immune system that detect infections and tissue damage as a first line of defense. PRRs sense so-called conserved non-self pathogen-associated molecular patterns (PAMPs) and host-derived danger signals (damage-associated molecular patterns or DAMPs) to initiate a host defense program through activation of various signal transduction pathways, which culminates in pathogen clearance and initiation of wound healing. Most of these pathways activate a transcriptional response leading to the up-regulation of nuclear factor κB (NF-κB), mitogen-activated protein kinase (MAPK) and interferon (IFN)-dependent genes, which encode cytokines, chemokines, adhesion receptors and others. However, for the maturation of the pro-inflammatory cytokines IL-1β and IL-18 into their biologically active and secreted forms, as well as for the induction of pyroptotic cell death of infected and damaged cells, additional processing in inflammasomes is required. Although inflammasome activation is beneficial for host defense, its dysregulation and in particular, excessive and uncontrolled release of IL-1β and IL-18, is linked to an increasing number of inflammatory and metabolic diseases. Therefore, the mechanism and regulation of inflammasome activation are under active investigation and relevant for multiple disciplines. Here, we discuss PRRs that are currently known to assemble inflammasomes, including the recently characterized PRR, the nucleotide-binding domain and leucine-rich repeat containing gene family member with a pyrin domain 7 (NLRP7, also know as *PYPAF3*, *NALP7*, *PAN7*, *NOD12*, *CLR19.4* and *HYDM*) and its role in inflammasome signaling and human disease.

* Corresponding author. Division of Rheumatology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA.
E-mail address: c-stehlik@northwestern.edu (C. Stehlik).

1286-4579/$ - see front matter © 2013 Institut Pasteur. Published by Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.micinf.2013.04.001

2. Inflammasomes

Inflammasomes are cytosolic multi-protein complexes that link pathogen recognition by specific cytosolic PRRs, including the NOD-like receptors (NLRs) and the Absent in melanoma 2 (AIM2)-like receptors (ALRs) to the activation of pro-inflammatory Caspases, including Caspase-1, -4 and -5 in humans and Caspase-1 and -11 (the Caspase-4 ortholog) in mice (Fig. 1) [1]. Caspase-1 mediates the proteolytic cleavage of pro-IL-1β and pro-IL-18, resulting in the bioactive, secreted form of these cytokines that act to initiate and perpetuate inflammatory host responses. Caspase-1 also promotes the release of other mediators, including IL-1α, IL-1Ra, HMGB1, FGF-2 and others through an unconventional secretion mechanism [2]. Infections by Gram-negative bacteria further require IFN-induced up-regulation of Caspase-11 upstream of Caspase-1 [3]. In addition, recent evidence shows that Caspase-8 can substitute for Caspase-1 under certain conditions [4,5]. Besides cytokine maturation, Caspase-1 also mediates inflammatory cell death (pyroptosis) of infected host cells [6]. Caspase-1 is recruited to activated PRRs by the central inflammasome adaptor apoptosis-associated speck-like protein containing a Caspase recruitment domain (CARD) (ASC, PyCard, TMS-1) [7,8]. Subsequently, Caspase-1 clustering causes its auto-activation through induced proximity. ASC is crucial for all inflammasomes activated by NLR family members containing a PYRIN domain (NLRPs) and ALRs (Fig. 1). However, NLRC4 (IPAF, CLAN), an NLR family member containing a CARD (NLRC), can directly recruit Caspase-1 [9–11], but ASC is nevertheless required for inflammasome activation in response to certain bacterial infections *in vivo*. In contrast to Caspase-1-dependent cytokine processing, which requires ASC and occurs in a singular distinct perinuclear inflammasome complex [12], Caspase-1-dependent pyroptosis proceeds independently of ASC and Caspase-1 autoproteolysis [13]. While the induced proximity mechanism of Caspase-1 activation is fairly well understood, the signaling events upstream of inflammasome-initiating PRRs of the NLRP, NLRC and ALR families are largely unknown.

2.1. NLR inflammasomes

22 *NLRs* are encoded in humans, while 34 *Nlrs* exist in mice. They are divided into five subfamilies based on their N-terminal effector domain: 1) *NLRA* (NLR containing an acidic domain), 2) *NLRB* (NLR containing a BIR domain), 3) *NLRC*, 4) *NLRP* and 5) *NLRX* (NLR with no homology to the N-terminal domain of any other NLR member). However, only a few members have so far been linked to inflammasome activation, including NLRP1, NLRP3 and NLRC4. NLRs sense and respond to a diverse array of infectious and sterile inflammatory signals with activation that promotes a conformational change, followed by receptor oligomerization, which is driven by nucleotide triphosphate binding and hydrolysis and the formation of the inflammasome platform upon recruitment of ASC-Caspase-1 and likely other proteins.

2.1.1. NLRP1

NLRP1 recognizes muramyl-dipeptide (MDP) and the lethal toxin (LT) from *Bacillus anthracis* [14,15]. While the recently generated *Nlrp1b* deficient mice confirmed the response to LT, they failed to show defects in the MDP response, which required Nlrp3 [16]. NLRP1 is unique among NLRs, due to the presence of an N-terminal PYRIN domain (PYD) and a C-terminal CARD, which not only allows it to recruit ASC and Caspase-1 through its PYD but also simultaneously to bind Caspase-5 directly through its CARD [1]. Of note is that the *NLRP1* gene has three paralog mouse genes, *Nlrp1a*, *Nlrp1b* and *Nlrp1c*, which all lack the PYD present in NLRP1. This might contribute to the conflicting observations

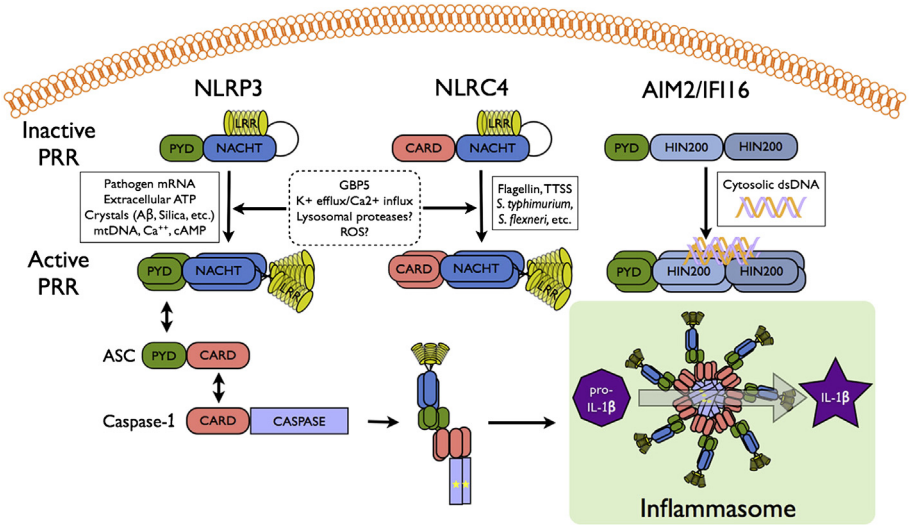

Fig. 1. Model for inflammasome activation. Stimuli that activate known inflammasomes are indicated, which cause oligomerization of the respective PRR. In the case of NLRs, oligomerization is induced by NACHT domain-mediated NTP binding. Subsequently, ASC and Caspase-1 are recruited by PYD–PYD and CARD–CARD interaction, respectively, which results in assembly of the inflammasome platform and activation of Caspase-1, as depicted by an asterisk. Proteolytically active Caspase-1 then converts pro-IL-1β and pro-IL-18 into their bioactive, mature forms.