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Commentary

The emerging role of human PYHIN proteins in innate immunity: Implications for health and disease

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ABSTRACT

The innate immune response depends on the ability of immune cells to detect pathogens through germline-encoded pattern recognition receptors (PRRs). Recently discovered PRRs include some members of the Pyrin and HIN domain (PYHIN) family, which are encoded on an interferon-inducible gene cluster located on chromosome 1q23. There are five human PYHIN proteins; Absent in melanoma 2 (AIM2), IFN-γ inducible protein 16 (IFI16), Myeloid cell nuclear differentiation antigen (MNDA), Pyrin and HIN domain family member 1 (PYHIN1) and the recently identified Pyrin domain only protein 3 (POP3). Early studies reported roles for these proteins in cell cycle control, tumour suppression and transcriptional regulation. AIM2 and IFI16 have now been shown to be immune sensors of non-self DNA, such as that produced by viruses in infected cells. AIM2 binds DNA to activate the inflammasome, while IFI16 detection of DNA can lead to the up-regulation of type I interferons or inflammasome activation. Recent studies have shown how IFI16 senses DNA viruses, and also how viruses evade detection by IFI16, while structural studies have greatly advanced our understanding of how AIM2 and IFI16 bind DNA to activate these immune responses. Furthermore, following the identification of POP3, interplay between members of this gene cluster has been established, with POP3 acting as a negative regulator of the AIM2 and IFI16 inflammasomes. In this review we discuss the current understanding of how PYHIN proteins function in innate immunity, their role in disease and the therapeutic possibilities that arise as a result.

1. Introduction

The innate immune system is composed of germline-encoded pattern recognition receptors (PRRs) that collectively serve as sensors for monitoring the extracellular and intracellular compartments for signs of infection or tissue injury. These PRRs, which are responsible for the detection of pathogen associated molecular patterns (PAMPs) which signal the presence of a pathogen, and damage associated molecular patterns (DAMPs) which signalling tissue injury, include the Toll-like receptors (TLRs), the retinoic acid inducible gene-like receptors (RLRs) and the nucleotide oligomerisation domain-like receptors (NLRs) [1]. Recently the classification of a new group of PRRs has been proposed. These are the AIM2-like receptors (ALRs) that comprise some members of the PYHIN family, namely human AIM2 and IFI16 and murine p204 [2].

The ALRs are intracellular innate immune sensors responsible for the detection of DNA. As a pathogen-derived PAMP, DNA is capable of stimulating protective immunity to infection while the erroneous detection of self-DNA, where DNA likely acts as a DAMP, can provoke excess inflammation and autoimmunity. The human ALRs AIM2 and IFI16 are encoded on an interferon (IFN)-inducible gene cluster found on chromosome 1q23. This region also encodes three other PYHIN proteins; MNDA, PYHIN1 and POP3 [3–6]. While this region encodes five proteins in humans, other mammals have variable family expansions, with at least thirteen family members present in mice [7]. Collectively these proteins are referred to as PYRIN and HIN domain-containing (PYHIN) proteins since they possess an N-terminal PYRIN (PYD) domain and in most cases at least one C-terminal hematopoietic interferon-inducible nuclear

Abbreviations: AIM2, absent in melanoma 2; ALR, AIM2-like receptor; ASC, apoptosis-associated speck-like protein containing a CARD; CARD, caspase activation and recruitment domain; cGAMP, cyclic GMP-AMP; cGAS, cGAMP synthase; DAI, DNA-dependent activator of IFN-regulatory factors; DAMP, damage associated molecular pattern; EBV, Epstein–Barr virus; HIN, hematopoietic interferon-inducible nuclear antigen; HIV-1, human immunodeficiency virus 1; HSV-1, herpes simplex virus 1; IFI16, IFN-γ inducible protein 16; IFN, interferon; IL, interleukin; ISG, immune stimulated gene; KSHV, Kaposi's sarcoma-related herpes virus; MNDA, myeloid cell nuclear differentiation antigen; MTB, *Mycobacterium tuberculosis*; NLR, nucleotide oligomerisation domain-like receptor; PAMP, pathogen associated molecular pattern; PYD, pyrin; PYHIN, pyrin and HIN domain family member; POP3, pyrin domain only protein 3; PRR, pattern recognition receptor; RLR, retinoic acid inducible gene-like receptor; SLE, systemic lupus erythematosus; STING, stimulator of interferon genes; TLR, toll-like receptor; YY1, ying yang 1.

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antigen with 200 amino acid repeats (HIN-200 or HIN) domain (Fig. 1). The PYD domain (also known as DAPIN or PAAD domain) belongs to the death domain superfamily and is an alpha-helical motif that forms homotypic interactions with other PYD containing proteins. The 200 amino acid DNA binding HIN domain is classified into three subtypes, termed A, B and C, based on consensus motifs [8]. POP3, the most recent member of this gene cluster to be identified, lacks the HIN domains found in other PYHIN proteins [3].

The PYHIN proteins have been shown to localise to both the nucleus and cytosol. AIM2 and POP3 are predominantly cytosolic proteins, while IFI16, MNDA and PYHIN1 are predominantly found in the nucleus owing to the presence of an N-terminal nuclear localisation sequence (NLS) [3,9]. However, other factors such as acetylation or the presence of stimulatory DNA (in the case of IFI16), or the onset of apoptosis (in the case of MNDA), can also influence their cellular localisation [10–12].

Due to recent exciting discoveries demonstrating roles for some PYHIN proteins as innate immune PRRs, in this review we re-visit the functions of these proteins. Here we will focus on the human PYHINs, discussing earlier studies on this protein family, their new roles in DNA sensing and transcriptional regulation, the mechanisms by which these events occur and possible approaches to targeting PYHINs therapeutically.

2. Early research on the human PYHINs

Prior to discoveries demonstrating that members of the PYHIN family function in pathogen recognition, studies focused on roles for these proteins in cell growth, cell cycle control, cell differentiation, tumour suppression, apoptosis, and the DNA damage response.

MNDA, the first human PYHIN family member discovered, was identified in HL-60 cells as a 55 kDa protein that is expressed predominantly in the nucleus and specifically in cells of the myeloid lineage [13]. Early studies into the role of MNDA suggested an involvement in myeloid differentiation. This idea was supported by studies revealing that MNDA can bind nucleolin and nucleophosmin [14,15], both of which have been shown to be involved in the maturation and biosynthesis of ribosomes. The noted nuclear localisation, and lineage- and stage- specific expression of MNDA suggested that this PYHIN protein may play a role in regulating gene transcription. MNDA has been shown to bind to the transcription factor ying yang 1 (YY1), forming a ternary complex along with the YY1 target DNA. The interaction between MNDA and YY1 increases the affinity of YY1 for its target DNA and decreases its rate of dissociation [16]. This means that cellular levels of MNDA could have a dramatic effect on the transcription of several genes, highlighting its potential as a key regulator of gene expression. Indeed, retroviral mediated expression of MNDA in K592 cells, which normally lack MNDA, correlated with induction of delta-like 1 (DLK1), whose expression is essential for normal haematopoiesis, and specifically for myeloid cell development [17]. MNDA itself has also been proposed to act as a transcription factor in monocytes [18] and this is supported by a more recent study demonstrating that MNDA can directly bind double stranded DNA (dsDNA) [19]. A possible role for MNDA in neutrophil apoptosis has also been proposed. Thus during apoptosis, MNDA is cleaved by caspases and then relocalises to the cytosol where it accumulates and associates with the anti-apoptotic protein myeloid cell leukaemia 1 (MCL1). This leads to MCL1 degradation, resulting in apoptosis caused by mitochondrial dysfunction [12]. This relocalisation of MNDA to the cytosol is thought to be required for proper execution of apoptosis and suggests that reduced cytoplasmic accumulation of MNDA contributes to suppression of neutrophil apoptosis. Furthermore, in septic patients cytoplasmic accumulation and cleavage of MNDA in neutrophils was dramatically impaired [12].

The second human PYHIN family member identified was IFI16. IFI16 migrates as three distinct protein species (IFI16A, B and C) on SDS-PAGE, the most abundantly expressed and commonly studied isoform being the B form. The three isoforms are generated as a

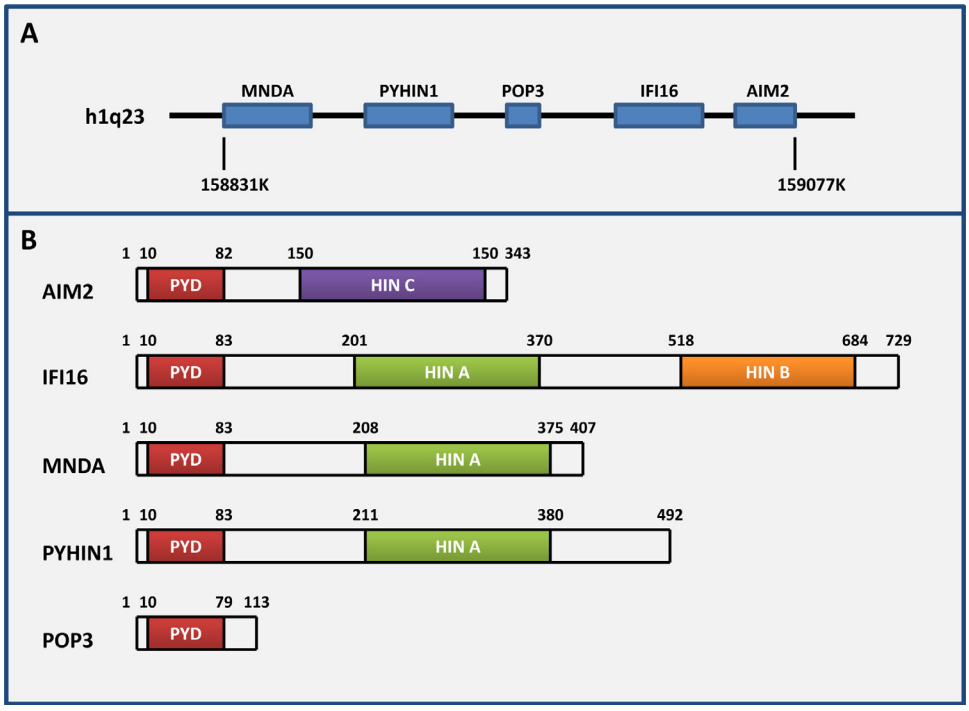

Fig. 1. The human PYHIN protein family. (A) Schematic representation of the PYHIN gene cluster on human chromosome 1q23. The approximate locations of the genes are shown. (B) Domain organisation of the proteins of the PYHIN gene cluster. The five PYHIN proteins each contain an N-terminal PYRIN domain (PYD), with some also having one or more C-terminal DNA binding HIN domains. These are classed as one of three subtypes; HIN A, HIN B or HIN C.

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