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Review

Inherited anomalies of innate immune receptors in pediatric-onset inflammatory diseases

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ABSTRACT

Pattern-recognition receptors (PRRs) can detect various pathogen-associated molecular patterns such as carbohydrates, nucleic acids or bacterial peptides and play a major role in both innate and adaptive immunity. In physiological conditions, the engagement of PRRs triggers the production of proinflammatory cytokines and promotes pathogen destruction. Inappropriate stimulation or defective regulation of PRR has been recently evidenced in several inherited inflammatory disorders. This new field of childhood-onset inflammatory diseases encompass the so-called type-I interferon-related diseases and autoinflammatory diseases.

Contents

Abbreviations: ACP5, Acid phosphatase 5; ADAR1, Adenosine deaminase RNA-specific 1; AGS, Aicardi-Goutières syndrome; ALRs, AIM2-like receptors; AIM2, Absent in melanoma 2; ASC, Apoptosis-associated speck-like protein containing a CARD; CANDLE, Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CAPS, Cryopyrin-associated periodic syndrome; CARD9, Caspase recruitment domain family member 9; CGAS, Cyclic GMP-AMP synthase; CLRs, C-type-lectin receptors; DAI, DNA-dependent activator of IRFs; FCL, Familial chiblain lupus; FMF, Familial Mediterranean fever; HSV-1, Herpes virus simplex-1; IKK, IκB kinase; IFI16, IFN-gamma-inducible protein 16; IFIH1, Interferon-induced helicase C domain-containing protein 1; IFNAR, IFNα/β receptor; IRAK4, Interleukin-1 receptor-associated kinase 4; IRF, IFN regulatory factor; ISRE, IFN-stimulated response elements; JAK, Janus-kinase; JMP, Joint contractures muscle atrophy, microcytic anemia, panniculitis and lipodystrophy; LUBAC, Linear ubiquitination chain assembly complex; MAPK, Mitogen-activated protein kinase; MAVS, Mitochondrial antiviral signaling protein; MDA5, Melanoma differentiation-associated protein 5; Myd88, Myeloid differenciation primary response 88; NLRs, NOD-like receptors; NLRC3, NLR family CARD domain containing 3; NLRP3, NLR family pyrin domain containing 3; NOD2, Nucleotide-binding oligomerization domain containing 2; PAMPs, Pathogen-associated molecular patterns; PFAPA syndrome, Periodic fever aphthous stomatitis, pharyngitis and adenitis syndrome; PID, Primary immunodeficiency; PRRs, Pattern Recognition Receptors; RIG-I, Retinoic acid-inducible gene 1; RLR, sRIG-I-like receptors; SAMHD1, SAM domain and HD domain 1; SAVI, STING-associated vasculopathy with onset in infancy; SKIV2L, Superkiller viralicidic activity 2-like (S. cerevisiae); SLE, Systemic lupus erythematous; SMS, Singleton-Merten syndrome; SoJIA, Systemic-onset juvenile idiopathic arthritis; SPENCD, Spondyloenchondrodysplasia; STAT1, Signal transducer and activator of transcription 1; STING, Stimulator of type-I IFN gene; TBK1, TANK-binding kinase 1; THES, Trichohepatoenteric syndrome; TIRAP, Toll-interleukin 1 receptor (TIR) domain containing adaptor protein; TLRs, Toll-like receptors; TNFα, Tumor necrosis factor α; TRAF3, TNF receptor-associated factor 3; TRAP, Tartrate resistant acid phosphatase; TRAPS, TNF receptor-associated periodic syndrome; TREX1, 3-prime repair exonuclease 1; TRIF, TIR-domain-containing adapter-inducing IFN-β; UNC93B1, Unc-93 homolog B1.

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1. Introduction

A fundamental function of innate immunity is to allow detection of infectious agents. This function is largely assumed by a limited range of proteins acting as sensors in immune and non-immune cells that can recognize and bind to a wide variety of pathogen-associated molecular patterns (PAMPs). Several classes of pattern-recognition receptors (PRRs) have been identified [1]. Depending on their expression pattern, their cellular localization and their structure, these sensors have been classified as Toll-like receptors (TLRs), C-type lectin receptors (CLRs), NOD-like receptors (NLRs), and cytosolic nucleic acid sensors such as RIG-I-like receptors (RLRs) and AIM2-like receptors (ALRs). The engagement of the latter sensors results in the production of type-I interferons (IFN). Over the past 20 years, a large number of genetic disorders caused by mutations in genes encoding innate sensors have been identified. These mutations cause primary immunodeficiencies (PID) or inflammatory diseases depending on the impact of the mutation on the function of innate sensors. This review will focus on pediatric-onset inflammatory diseases due to inherited anomalies in the innate immune response with a special highlight on diseases linked to upregulation of type-I interferon, so-called interferonopathies.

2. Innate immune sensors

Innate immune receptors can be divided into two groups depending on their localization in the cell and as consequence by which PAMPs-mediated inflammatory response they can trigger.Membrane PRRs such as TLRs (TLR1, TLR2, TLR4, TLR5 and TLR6), CLRs (Dectin-1, Dectin-2) and Mincle are sensors for motifs mainly found in extracellular bacteria and fungi (lipopolysaccharide, lipoproteins, carbohydrates, etc.). TLRs are type-I transmembrane proteins that contain an ectodomain composed of numerous copies of leucin-rich repeat for PAMPs recognition and an intracellular Toll-interleukin 1 (IL-1) receptor (TIR) domain, which interacts with distinct adaptor molecules such as MyD88 and TRIF, as well as TRAM and TIRAP, which are considered as sorting adaptors for the recruitment of MyD88 and TRIF [2]. The MyD88-dependent pathway is used by all TLRs except TLR3. MyD88-dependent signal transduction activates the recruitment of Interleukin-1 (IL-1) Receptor-associated Kinase (IRAK) complex and subsequently activates NF-κB and MAP kinases to induce the production of pro-inflammatory cytokines (e.g. TNFα, IL-6, IL-1β). TLR4 is the only TLR capable to use all adaptors and to trigger both MyD88- and TRIF-dependent pathways.

CLRs are key sensors of antifungal immunity. This heterogeneous family of transmembrane and soluble receptors, defined by a characteristic C-type lectin domain, is likely to be wider than previously thought [3]. The CLR Dectin-1 found on myeloid dendritic cells (DCs) plays a very important role in antifungal immunity by controlling IL-1β processing via the formation of caspase-8 inflammasome [4]. Mutations in these membrane sensors or in their downstream signaling pathways lead to PID. For example, MyD88- or IRAK4-dependent pathway defects predispose children to pyogenic bacterial diseases and TLR3 deficiency to Herpes simplex virus encephalitis [5].

Antiviral immunity is dependent partly on the detection of nucleic acids by endosomal TLRs (TLR3, TLR7, TLR8 and TLR9), expressed in immune cells with a specific distribution [2]. B cells and plasmacytoid DCs (pDCs) express TLR7 and TLR9 and myeloid DCs primarily express TLR3 and TLR8. Upon engagement, these receptors induce both inflammatory cytokines and type-I IFNs by recruiting adaptor molecules MyD88 (for TLRs 7/8 and 9) and TRIF (for TLR3), which act via IRF7 and IRF3 respectively. When exposed to viral nucleic acids, pDCs are the most type I interferon-producing cells in the body. These cells have as consequence a crucial role in inducing antiviral immunity as well as in promoting pathological processes when the system of regulation is defective like in numerous autoimmune diseases [6]. Ligands for endosomal TLRs include double stranded RNA (dsRNA) for TLR3, single stranded RNA (ssRNA) derived from RNA viruses for TLR7/8, and unmethylated cytosine-guanine (CpG) DNA motifs and the recently discovered RNA:DNA hybrids [7] for TLR9. Nucleic acids are also recognized in the cytosol by two cell-intrinsic systems: RIG-like receptors (RLRs) for RNA and specialized DNA-sensors [8].

RLRs include RIG-I, melanoma differentiation-associated gene 5 (MDA5) and laboratory of genetics and physiology 2 (LGP2). RIG-I and MDA5, contains two amino (N) terminal CARDs, a central ATPase and helicase domain and a carboxy (C) terminal regulatory domain. Upon interaction with intracytoplasmic dsRNAs [9], these 2 proteins activate type-I IFN production via their CARD domains, and through the adaptor protein MAVS and the cytosolic kinases IKK and TBK1. It was firstly thought that LGP2 functions as a negative regulator of MDA5 and RIG-I but it seems that in certain condition this receptor could directly trigger the production of type-I IFN [10].

Several cytosolic DNA sensors, such as the cyclic-GMP-AMP synthase (cGAS) [11], can also induce type-I IFN production after recognition of non-self or self-antigens. The endoplasmic reticulum transmembrane protein STING (encoded by *TMEM173*) is a crucial adaptor in this pathway, allowing the activation of the downstream molecules IRF3 and NF-κB through the kinases TBK1 and IKK respectively and leading to the production of type-I IFNs as well as inflammatory cytokines [8]. A well-known negative regulator of this STING-dependent antiviral response is the 3′-5′ DNA exonuclease Trex1, but the regulatory system of this pathway appears to be much more complex than previously thought [12]. Indeed, some interactions between NLRs and the STING pathway are likely to exist since NLRC3 was proved to be a negative regulator of the DNA sensor STING [13]. STING is also able to sense directly cyclic dinucleotides [14]. Other putative DNA sensors are suggested like DNA-dependent activator of IRFs (DAI), DNA-PK and the member of the PYHIN protein family IFI16 but additional studies have to prove their role [8].

The RNA polymerase III/RIG-I pathway allows the detection of A/T-rich DNA that activates the innate immune response through transcription of DNA by cellular RNA polymerase III [15].

The different pathways of nucleic acid sensing lead to the activation of an IFN regulatory factor (IRF) and induction of type-I IFN production, allowing the host to trigger appropriate innate and adaptive responses against a broad range of pathogens. DNA sensing pathways may also recognize self-DNA, which could lead to autoimmune disorders. To

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