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PATTERN-RECOGNIZING RECEPTORS AND THE INNATE IMMUNE RESPONSE TO VIRAL INFECTION

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The innate immune response to viral pathogens is crucial in mobilizing defensive reactions of an organism during the development of an acute viral infection. Cells of the innate immunity system detect viral antigens due to genetically programmed pattern-recognition receptors (PRRs), which are located either on the cell surface or inside the certain intracellular components. These image-recognizing receptors include Toll-like receptors (TLRs), retinoic acid-inducible gene I-like receptors (RIG-I-like receptors), nucleotide oligomerization domain-like receptors (NOD-like receptors), also known as NACHT, LRR and PYD domains of the protein, and cytosolic DNA sensors. The trigger mechanisms for these receptors are viral proteins, and nucleic acids serve as activators. The presence of PRRs that are responsible for the determination of viral antigens in cellular components allows the cells of innate immunity to recognize a wide range of viral agents that replicate in various cellular structures, and develop an immune response to them. This article summarizes the disparate data presented in modern English literature on the role of PRRs and the associated signaling pathways. Understanding the recognition of viral pathogens required triggering a cascade of cytokine and interferon production provides insights into how viruses activate the signal paths of PRRs and the effect of the interaction of viral antigens and these receptors on the formation of the antiviral immune response.

KEY WORDS: pattern-recognition receptors, Toll-like receptors, RIG-I-like receptors

ПАТЕРН-РОЗПІЗНАВАЛЬНІ РЕЦЕПТОРИ ТА ПРИРОДЖЕНА ІМУНОЛОГІЧНА ВІДПОВІДЬ НА ВІРУСНУ ІНФЕКЦІЮ

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Вирішальне значення в мобілізації захисних реакцій організму протягом розвитку гострої вірусної інфекції має вроджена імунологічна відповідь на вірусні патогени. Клітини системи вродженого імунітету виявляють вірусні антигени за допомогою генетично запрограмованого патерн-розпізнавання рецепторів (PRRs), які розташовані або на поверхні клітини, або всередині певних внутрішньоклітинних компонентів. Ці образ-розпізнавальні рецептори включають Toll-подібні рецептори (TLRs), RIG-I-подібні рецептори (RLRs), NOD-подібні рецептори, також відомі як домени NACHT, LRR та PYD білків, та цитозольні ДНК-сенсори. Пусковим механізмом для цих рецепторів є вірусні протеїни, а активаторами слугують нуклеїнові кислоти. Наявність PRRs, що відповідають за визначення вірусних антигенів у клітинних компонентах, дає клітинам природженого імунітету можливість розпізнавати широкий спектр вірусних агентів, що реплікуються в різних клітинних структурах, і виробляти імунологічну відповідь на них. В даній статті узагальнено розрізнені дані, які представлені в сучасній англомовній літературі, щодо ролі PRRs та пов'язаних з ними сигнальних шляхів. Розуміння розпізнавання вірусних патогенів, необхідних для запуску каскаду продукції цитокинів і інтерферонів, дозволяє збагнути, як віруси активізують сигнальні шляхи PRRs і як впливає взаємодія вірусних антигенів і цих рецепторів на формування противірусної імунної відповіді.

КЛЮЧОВІ СЛОВА: патерн-розпізнавальні рецептори, Toll-подібні рецептори, RIG-I-подібні рецептори

ПАТЕРН-РАСПОЗНАЮЩИЕ РЕЦЕПТОРЫ И ВРОЖДЕННЫЙ ИММУННЫЙ ОТВЕТ НА ВИРУСНУЮ ИНФЕКЦИЮ

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Решающее значение в мобилизации защитных реакций организма во время развития острой вирусной инфекции имеет врожденный иммунный ответ на вирусные патогены. Клетки системы врожденного иммунитета обнаруживают вирусные антигены благодаря генетически запрограммированным образ-распознающим рецепторам (PRRs), которые располагаются либо на поверхности клетки, либо внутри определенных внутриклеточных компонентов. Эти образ-распознающие рецепторы включают в себя Toll-подобные рецепторы (TLRs), RIG-I-подобные рецепторы (RLRs), NOD-подобные рецепторы, известные также как NACHT, LRR и PYD домены белка, и цитозольные сенсоры ДНК. Пусковым механизмом для этих рецепторов являются вирусные протеины, а активаторами служат нуклеиновые кислоты. Наличие PRRs, отвечающих за определение вирусных антигенов в клеточных компонентах, дает клеткам врожденного иммунитета возможность распознать широкий спектр вирусных агентов, реплицирующихся в различных клеточных структурах, и выработать в отношении их иммунный ответ. В данной статье обобщены разрозненные данные, представленные в современной англоязычной литературе, относительно роли PRRs и связанных с ними сигнальных путей. Понимание распознавания вирусных патогенов, необходимых для запуска каскада продукции цитокинов и интерферонов, позволяет получить понимание того, как вирусы активируют сигнальные пути образ-распознающих рецепторов и какое влияние взаимодействие вирусных антигенов и этих рецепторов оказывает на формирование противовирусного иммунного ответа.

КЛЮЧЕВЫЕ СЛОВА: образ-распознающие рецепторы, Toll-подобные рецепторы, RIG-I-подобные рецепторы

INTRODUCTION

Cells of the innate immune system use pattern-recognition receptors (PRRs) that identify pathogen-associated molecular patterns (PAMPs) located on the surface of viral cells and differ from those of the host cell to identify viral pathogens. The ability to identify nucleic acids has become a major component of the antimicrobial link of the immune system. A wide range of pathogens are identified by recognizing their genome or nucleic acids that accumulate during the replication of viruses. PRRs are activated in response to viral molecules such as 5′-triphosphate RNA, as well as viral DNA, which is determined by sensory elements located in the cytoplasm.

The main PRRs are Toll-like receptors (TLRs). They are type 1 transmembrane proteins providing communication between the plasma membrane and endosomal vesicles. The main function of TLRs is the detection of PAMPs in the extracellular space. Receptors located on the plasma membrane are involved in the detection of hydrophobic lipids and proteins, and receptors located in endosomes are able to detect nucleic acids. Such a division allows cells of the innate immune system to identify components of the viral envelope located on the cell surface, such as components of the fusion mechanism, and nucleic acids located in the endosomes. Entering the cytoplasm viral components enter the area monitored by RIG-I-like receptors, NOD-like receptors and cytosolic DNA sensors, such as members of the AIM2 family. Similar to TLRs, RIG-I-like receptors and cytosolic DNA sensors regulate the expression of transcription factors necessary for the production of interferons and cytokines. And NOD-like receptors and members of the AIM2 family, by contrast, activate the process of maturation of IL-1β and IL-18 by activating caspase 1. Induction of immature forms of IL-1β and IL-18 occurs through the activation of TLRs signaling pathways, and NOD-like receptors serve as a kind of «control mechanism» that regulates and activates the release of these powerful effectors. Many PRRs are involved in the activation of the adaptive immune system by enhancing expression of the major histocompatibility complex class II and stimulating the expression of co-stimulating molecules CD40, CD80 and CD86 in addition to the release of pro-inflammatory components.

TOLL-LIKE RECEPTORS

10 types of TLRs have been identified in humans, and 13 types – in mice, 9 of them (TLRs of types 1–9) are identical. TLRs of 1, 2, 4, 5 and 6 types (TPRs 1, 2, 4, 5, 6) are located on the cytoplasmic membrane, and TLRs 3, 7, 8 and 9 are endosomal. All TLRs have a common structure and consist of extracellular repeats rich in leucine and the Toll/Interleukin-1 Receptor (TIR) cytoplasmic domain [1]. These receptors transmit a signal differentiating the adapter proteins Mal (MyD88 adapter-like), also known as TIR domain-containing adapter proteins (TIRAPs) and Myeloid differentiation primary response gene 88 (MyD88), gene for primary myeloid differentiation 88, and/or TIR-domain-containing adapter inducing interferon-β (TRIF) and Trif-related adaptor molecule (TRAM) [1]. Adapters initiate the launch of signaling cascades, culminating in activation of the nuclear factor κB (NF-κB), mitogen-activated protein kinase (MAPK) and interferon regulatory factors 1, 3, 5 and 7 (INF-1, -3, -5 and -7) [2]. The combination of these transcription factors promotes not only the expression of interferons, cytokines and chemokines, but also affects the maturation and survival of cells.

Toll-like receptor signaling pathways

All TLRs, apart from TLR 3, require the presence of MyD88 for their activation [3–4].

TLR 3 is not capable of MyD88 capturing and interacts with the TRIF through the adapter protein. TRIF has the ability to directly bind TRAF6 and induce NF-κB along a path similar to MyD88. TRIF is also capable of involving the receptor-interacting protein-1 (RIP-1) in the process in contrast to MyD88. RIP-1 interacts with TRAF6 that leads to powerful activation of NF-κB. TRAF3 is the third protein attracted to TRIF. It binds with TANK-binding kinase-1 (TBK1) and IKKi and is a necessary component of the production process of interferon type 1. This allows them to undergo a dimerization procedure and penetrate the nucleus, where they interact with NF-κB and activator protein 1 (AP-1), that in turn leads to the transcription of the target gene. The study, which included children with non-functioning MyD88 proteins, showed that patients with this pathology are predisposed to develop recurrent pyogenic bacterial infections [5]. Patients with IRAK-4 deficiency and with a defect of UNC-93B1, a protein that is involved in the transport of TLRs 3, 7, 8, and 9 into endosomes, had an increased susceptibility to the herpes simplex virus type 1 with predominant brain damage [6–7]. Peripheral blood mononuclear cells and fibroblasts obtained from these patients demonstrated a decrease in type 1 interferon activity in response to the introduction of HSV-1, accompanied by enhancement of viral replication [7].

Expression and activity of Toll-like receptors

The severity of the inflammatory reaction caused by viral PAMPs depends on the following factors.

1. Cellular expression of TLRs varies depending on cell type. It is known that macrophages express a large number of TLRs 2 and 4, while plasmacytoid dendritic cells (pDCs) mainly produce TLRs 7 and 9 [1];
2. The expression level also varies between species; for example, TLR 9, expressed in the human body by just a few cell types, is well represented in mice;
3. The reaction to identical viral PAMPs can vary between cell types, both in the nature of the produced effector molecules and in the response kinetics.

INTRACELLULAR NUCLEIC ACID SENSORS

TLRs play an important role in the detection of viral PAMPs that present both on the surface of cells and in endosomes. The identification of additional mechanisms of antiviral protection has revealed many classes of innate sensors that play an important role in the purification of viruses that replicate and locate in the cytosol. Specialized classes of cytosolic nucleic acid sensors, called RIG-I like receptors (RLRs), are capable of recognizing intracellular RNA that penetrates into the cytosol during virus introduction or accumulates during viral replication, as well as DNA that is inside cytosol.

The RLRs family includes three DExD/H box RNA helicases: retinoic acid-inducible gene (RIG-I), melanoma differentiation-associated gene 5 (MDA-5), and LGP-2 [8–11].

RIG-1 and MDA-5 consist of N-terminal caspase activation and recruitment domains (CARDs), the following helicase RNA DExD/H box domain, which has ATP-ase activity, and the C-terminal repressor domain. RIG-I controlled by its regulatory domains is

inactive in the cytoplasm in the absence of pathogenic activation. Conformational changes occur in RIG-1, when viruses enter the body, RIG-1 dimerizes as a result [12]. The activated multimeric form of RIG-1 or MDA5 interacts with the mitochondrial antiviral-signaling protein (MAVS) located on the outer mitochondrial membrane. MAVS activates IKK-related kinase after capturing RIG-I or MDA5, resulting in the transcription of interferons type 1. Also, MAVS also activates NF-kB by recruiting a tumor necrosis factor receptor type 1-associated death domain protein (TRADD), the FAS-associated protein with the death domain (FADD), caspase-8 and caspase-10 [13–16]. LGP-2 does not contain N-terminal DARK domains, but consists only of the helicase RNA domains. It is assumed that it acts as a negative regulator of other RLRs [9, 12].

Recognition of RNA RIG-like receptors

RLRs are important components of antiviral protection for many types of cells, including fibroblasts, epithelial cells and normal dendritic cells. Studies have shown that only MDA-5 is responsible for the production of interferon through the stimulating of polyI: C [17–18]. RIG-I does not have the ability to recognize the 5'PPP-ssRNA of the host cell; they use the 5 'end of the transcript to recognize the virus RNA and the host cell. In contrast, MDA-5 uses not the 5 'end of the transcript, but the length of the RNA sequence for recognition of the virus RNA and the host cell; long dsRNAs are usually absent in the host cell, and, thus, act as a ligand for MDA-5. RIG-I is also able to recognize short dsRNA, which is a by-product of viral replication, in addition to recognizing 5'-triphosphate RNA.

RIG-I is involved in the recognition of vesicular stomatitis virus (VSV), rabies virus, Newcastle disease virus, respiratory syncytial virus, measles virus, influenza A and B viruses, hepatitis C virus (HCV), Japanese encephalitis virus and Ebola virus [18-19]. MDA-5 is involved in the recognition of CMV, Theiler's encephalomyelitis virus and Mengo virus [20]. All of these viruses do not contain 5'-triphosphate RNA, but are capable of producing long dsRNA, that provides additional evidence that MDA-5 distinguishes RNA based on sequence length, rather than 5'-triphosphate. It is proven that Dengue virus, West Nile virus and reovirus transmit signals through the use of a combination of RIG-I and MDA-5.

DDX3

A recent study described the participation of another representative of the DExD/H box family of RNA helicase, DDX3, in the antiviral response. It was found that the K7 protein of the measles virus inhibits the induction of INFβ through the binding to DDX3, which in turn led to the discovery of the positive role of DDX3 in activating the RLR signaling pathway. DDX3 binds to polyI: C and viral RNA penetrating into the cytosol and binds to MAVS/IPS-1, whereby it takes part in activating the production of INFβ, enhances RNA recognition, forming a complex with RIG-I and MAVS that induces interferon production.

DNA cytosolic sensors

Scientists knew that pathogen DNA is capable of activating fibroblasts and stimulating the production of IFN type 1 even before the discovery of TLR 9.

Cytosolic recognition of DNA and RNA leads to activation of TBK1, IRF-3 and production of IFN type 1. However, signaling pathways connecting upstream DNA and TBK1 sensors are currently poorly understood. TBK1 interacts with DDX3, a DEAD box RNA helicase, which regulates the transcription of IFNβ through the IRF-3.

DAI

DNA-dependent activator of IFN-regulatory factors (DAI) was one of the first cytosolic DNA sensors detected. It consists of two related domains capable of recognizing the left-twisted Z-forms of DNA and its B-forms. DAI increased the dose-dependent production of IFN type 1in the L929 cell culture during the exogenous expression after stimulation of the B and Z forms of DNA. Similarly, turning off DAI by means of ssRNA disrupts the production of type 1 IFN in response to DNA, 45 bp interferon-stimulating DNA (ISD) of Listeria and herpes viruses, as well as HSV-1. It was also found that the production of IFN type 1 also depends on DAI during the CMV introducing. These results suggest that the role of DAI may be specific for each individual cell type, it plays an excessive role in probing of cytoplasmic DNA, and that other sensors must be needed to induce these responses.

Pol III RNA and LRRFIP1

Viral RNAs trigger the production of IFN type 1 by activating RIG-I. It has been proven that the B-form of dsDNA in human cells can

also induce the production of INFβ in a way that depends on the adapter molecule RIG-I MAVS [21–22]. DNA with a high content of antibodies is transcribed into 5'-pp RNA using RNA polymerase II, which in turn activates RIG-I [21].

Another regulator of DNA-controlled innate immune signal transmission, a leucine-rich repeat flightless-interacting protein 1 (LRRFIP1) has recently been described in addition to DAI and Pol III RNA. It inhibits the production of IFN 1 type induced by bacteria. Turning LRRFIP1 off inhibits the production of IFN in response to polyI: C stimulation, synthetic DNA, poly (dG:dC) and poly (dA:dT) stimulation, involving LRRFIP1 in the recognition of dsRNA, as well as B-and Z-forms of dsDNA.

IFI16

IFI16 was identified as a DNA-binding protein that interacts with dsDNA through the process of analyzing the immune responses to these dsDNA regions obtained from the HSV-1 genome. IFI16 is a member of the PyHIN protein family (containing the pyrin and HIN200 domains). The PHYIN family includes 4 representatives: IFIX, IFI16, MNDA and AIM2. They all contain one or more HIN200 domains that recognize DNA, as well as the pyrin domain. Turning IFI16 or p204 (a member of the PYHIN family of mice) off leads to a decrease in the intensity of the IFNβ response to these dsDNA. IFI 16 is localized in the nucleus, and in the cytosolic cellules of macrophages. IFI16 pooling is required for IFNβ production in response to DNA. Turning IFI16 and its homologue of p204 in mice off in mRNA leads to a decrease in the activation of IRF3 and NF-κB, and also leads to the IFNβ gene induction in cells once infected with HSV-1.

DDX9 and 36

DExD/H box RNA helicase – DHX9 and DHX36 are found in plasmacytoid dendritic cells. Activation of DHX9 leads to activation of IRF-7 and increased production of IFNα, and activation of DHX36 leads to activation of NF-κB and increased production of IL-6 and TNFα. Turning DHX9 and DHX36 off in mRNA inhibits cytokine production in response to DNA-containing HSV-1, while the response to an RNA-containing influenza A virus remains unchanged.

Inflammasomes, their types

The recognition of viral DNA is associated with the transcriptional induction of IFN type 1 and other pro-inflammatory cytokines, as well as with the launch of caspase-1-dependent maturation of pro-inflammatory cytokines IL-1β and IL-18. IL-1β is involved in the recruitment of innate immunity cells, T-lymphocyte activation and fever induction, and IL-18 increases the cytolytic activity and production of IFNγ by natural killer cells (NK cells), and also affects the recruitment and activation of neutrophils.

The production of IL-1β is controlled at the level of transcription, translation, maturation and secretion. Many cellular stimuli, including TLRs ligands, activate the transcription of pro-forms of IL-1β and IL-18. Maturation (i.e. cleavage) of pro-IL-1β and pro-IL-18 is catalyzed by cysteine protease of caspase-1. The activity of inflammatory caspase-1 is controlled by a large complex called «inflammasomes protein complex». Then active caspase-1 cleaves pro-IL-1β and pro-IL-18.

Inflammasomes AIM2 recognize their own and foreign cytosolic dsDNA, including viral DNA, through the HIN 200 domain. DNA recognition provokes the assembly of inflammasomes complexes. Upon DNA binding, AIM2 undergoes oligomerization and binds apoptosis-associated speck-like protein (ASC) through the interaction of pyrin-pyrin homotypic domains, which in turn recruits pro-caspase 1. Inflammasomes and AIM2 are an integral component of the innate recognition of DNA-containing viruses, CMV, as well as Francisella tularensis and Listeria monocytogenes.

NLRP 3 inflammasomes play an important role in the formation of a response to RNA-containing viruses, adenoviruses, and DNA-containing viruses. NLRP3 deficiency weakens the normal response of IL-1β and IL-18 to the influenza virus and is associated with a decrease in cell recruitment of the innate immune system [23].

CONCLUSIONS AND PROSPECTS FOR FUTURE STUDIES

The understanding of how the innate immune system detects viruses and triggers a cascade of antiviral reactions has increased significantly over the past decade. The discovery of Toll-like receptors and nucleic

acids led to the discovery of various cytosolic RNA and DNA receptors and their downstream signaling pathways. However, many cytosolic sensors play an excess role in the detection of viruses. Such excessive protection strategies have evolved to deal with the evasion mechanisms of detection inherent in viruses. Determining the function of newly identified pattern-recognizing receptors in the immune defense against viral infection is an important step in understanding of their unique or auxiliary contribution to the pathogenesis of viral protection.

The mechanisms of nucleic acid sensors operation, the aim of which is to distinguish their own nucleic acids from the nucleic acids of viruses, require clarification, as well as the process of recognition of viral RNA and DNA, which are becoming available for pattern-recognition receptors.

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