Review paper

RLR receptors – important elements of innate immunity

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Abstract

The paper presents the RLRs (RIG-I-like receptors) that are members of PRRs (pathogen recognition receptors) and are found on immunity system cells, binding to structures originating from germs, called as PAMP (pathogen-associated molecular patterns). PRRs are divided on secreted receptors, surface receptors engaged in phagocytosis and cell activating receptors or receptors expressed on immunity and other cells surface. RLRs belong to the third group of PRRs. Among RLRs there are RIG-I receptor (cytosolic double-stranded RNA helicases retinoic-acid-inducible gene I) i MDA5 receptor (melanoma differentiation-associated gene 5). Both RIG-I and MDA5 play a major role in recognition of RNA viruses in DCs, macrophages and fibroblasts. There has been shown that RIG-I binds 5'-triphosphorylated ssRNA and short dsRNA viruses whereas MDA5 preferentially recognizes longer-dsRNA. RLRs are receptors of innate immunity, that are very important in antiviral response. It seems that those receptors determine significant defense line in viral infection and restrict replication and invasion of pathogens.

Key words: *innate immunity, immunological response, receptors, RIG-I, MDA5, viruses.*

(Centr Eur J Immunol 2011; 36 (2): 117-119)

Despite their small size and rather small genomes, pathogenic viruses may have a detrimental impact onto the body. This is because they all encode proteins that are important to build components of such viruses and their replication, and additionally may encode proteins that prevent or inhibit antiviral response [1-3]. Such proteins ensure the entry of the virus, its replication, and then spreading across the organism. It is known that the virus cannot replicate by itself, as it depends on the functioning of the host's cell. The processes of viral entry in the cell, stimulation and regulation against the host's viral immunological response, result in complex series of interactions between the virus and the host's immune system. The host's immune systems have developed a number of varied cellular signal networks which participate in detection and building the macroorganism's response to viral infections. It was evidenced that in mammal cells, there are many specialised receptors responsible for infection recognition, including viral infections, which stimulate the body's response to new factors appearing in them. It must be observed that the antiviral immunological response principally takes place where it is participated in by pathogen recognition receptors (PRR) present in the immune system cells, ligands for which are the structures originating from pathogens, including viruses, referred to as PAMP (pathogen-associated molecular patterns), and which – in the case of viruses – are proteins (haemagglutination protein, fusion protein F, HSP and sheath protein), nucleic acid and small antiviral units [4-6].

PRR receptors can be divided into secreted receptors, namely opsonins, including immunoglobulins (Ig), complement (C), facilitating e.g. the process of phagocytosis and cytotoxicity; surface receptors also participating in phagocytosis, e.g. mannose receptor, CLR, Ig or directly binding the microorganism structure, e.g. for collectins; and cell activating receptors, present on the surface of immune system cells, although also on other cells – e.g. epithelial cells, endothelium, and these are TLR receptors (toll-like receptors) [7, 8], RLR (RIG-I-receptors), NLR (NOD-like receptors) [9], as well as TIM, TAM (T-cell immunoglobulin domain and mucin domain) [10, 11] and TRIM (tripartite motif-containing proteins) [8, 12]. It was evidenced that after binding to viral PAMP, PRR receptors initiate inter-cellular signal cascade, which results in activation of transcription factors, including IFN-regulatory factors (IRFs) and nuclear factor κβ (NF-κβ). It was determined that the transcription factors regulate expression of many

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genes, such as IRF – IFN-regulatory factors, and IFN-stimulated genes (ISGs), as well as other particles, including pro-inflammatory cytokines and chemokines, which are also involved in the generation of immunological response [13, 14]. Also, in many types of immune system cells, such PRR receptor activation stimulates antiviral "status", and additionally, such a situation strongly induces e.g. production of pro-inflammatory substances in antigen presenting cells. Among PRR receptors which participate in virus recognition and stimulation of immunological response, there are RIG-I-like receptors (RLR), present on the cell surface or in endosomal membranes, including RIG-I (cytosolic double-stranded RNA helicases retinoic-acid-inducible gene I) and MDA5 (melanoma differentiation-associated gene 5). RLR markers are composed of helical domain, which is responsible for recognition of viral RNA – RIG-I protein recognises 5'-triphosphate ssRNA and short dsRNA fragments of viruses, while MDA5 protein recognises poly I:C regions in dsRNA and longer dsRNA fragments [15, 16]. The family of RLR receptors indicates similarity to TLR receptors in the aspect of signal activation and induction of type I interferon genes [15, 16].

RIG-I and MDA5 receptors, belonging to RLR, as already mentioned, play an important role in recognition of viral RNA, particularly in dendritic cells (DC), macrophages and fibroblasts [9]. It was determined that RIG-I principally binds to viral 5'-triphosphate ssRNA, e.g. paramyxoviruses (parainfluenza type 3 virus), ortomyxoviruses (influenza virus) and short viral dsRNA chains, e.g. rotaviruses A, by stimulating type I IFN synthesis [9]. Moreover, the receptors also take part in recognition of RNA viruses, such as VSV (vesicular stomatitis virus) or JEV (Japanese encephalitis virus) [9]. In turn, MDA5 marker shows greater affinity to binding to longer dsRNA chains and recognises i.a. EMCV (encephalomyocarditis virus), Theiler's virus or Mengo virus [9]. Hence, mice deprived of RIG-I and MDA5 are unusually susceptible to infections with such viruses, including, in particular, VSV and EMCV [9]. The studies revealed [17] that infection of wild type cells with the Western Nile virus leads to induction of IRF3 genes and ISGs and various subtypes of interferons-α, while in a later phase of this infection, to expression of antiviral genes dependent on IFN. It was determined that in stimulation of immunological response against infections caused by the Western Nile virus, RIG-I receptor is very important, as confirmed by studies on cells deprived of this receptor. It was also evidenced that lack of MDA5 receptor in these cells blocks their capacity of responding to infections caused by the virus. It was proved that cells deprived of this receptor do not induce type I IFN synthesis in response to paramyxoviruses, ortomyxoviruses, and VSV [9, 18]. Furthermore, it was determined that in cells deprived of RIG-I receptor, infection with the influenza virus did not cause expression of IFN-β, as well as many interferon stimulated genes (ISGs) and antiviral mediators, such as IRF3 (interferon regulatory factor 3), STAT1 (signal transducer and activator of transcription 1), IFIT1 (IFN-induced protein with tetratripeptide repeats 1) and IFIT2 (IFN-induced protein with tetratripeptide repeats 2) [18].

Among the "changing image" of the viruses alone, which is necessary for their existence and causing infections in the macroorganism, their capability is important of blocking immunological response of the host or modulation of antiviral substance activity. An example of such a virus is the hepatitis C virus (HCV), which is capable of blocking the early natural immunological response of the host. It was evidenced that serine protease – NS3-NS4A, blocks activation of IRF3 (IFN-regulatory factor). The process is a result of cleavage of adapter protein TRIF (Toll/interleukin-1 [IL-1] receptor-domain-containing adapter protein inducing IFNβ), which is responsible for IRF3 and NF-$\kappa\beta$ activation, as a result of which TLR3 receptor is attached to kinases [19, 20]. It was also evidenced that HCV virus inhibits the capacity of RIG-I receptor to activate IRF3 [20-22], which is caused by cleavage of IPS1 protein (IFNB-promoter stimulator 1) and adapter protein for RIG-I [24-27]. There are also known studies regarding viruses that inhibit expression of interferon stimulated genes (ISG) [28]. The studies revealed clear suppressions of the genes in the key pathways of innate antiviral immunity, including the ones participated in by IRF3. An example here may be formed by philoviruses, which clearly inhibit genes in the key pathways of antiviral immunological response [28]. Furthermore, it was evidenced that such viruses as Zair, Ebola and Marburg, inhibit the expression of most ISG genes [28]. It was recorded that suppression of type I IFN response caused by pathogenic mammal viruses is related to quick spreading of the viruses, and greater frequency of their replication [29]. It was determined that virulence of highly pathogenic viruses, including of Zair or Ebola, is also related to their capacity of inhibiting antiviral response of the host, which may be a cause of the high level of the viral replication [30]. Another example of the virus that masks against the elements of the immune system is the cytomegaloviral disease virus, which reduces expressions of the MHC particle, and the herpes virus, which inhibits peptide transport at the TAP level to the reticulum, which reduces expression of MHC-peptide complexes and adenoviruses, which, by blocking the transcription of genes encoding MHC, decrease its expressions [4].

To conclude, it must be stated that RLR receptors are markers of innate immunity, which are a very important factor in antiviral response in mammals. In viral infections, it seems that the receptors and the related phenomena constitute an important line of defence, which limits replication and invasion of such pathogens. Despite the fact that the issue of antiviral immunity has been studies for many years, it seems that only the understanding of how PAMP

(dsRNA, ssRNA, CpGDNA, small antiviral units, haemagglutination protein, fusion protein F, HSP and sheath protein), present on the viruses, are detected by PRR receptors, and this has proved how important these elements are in the process of virus recognition and "building" antiviral immunity of the macroorganism.

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