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Review

Gene/environment interactions in the pathogenesis of autoimmunity: New insights on the role of Toll-like receptors

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ABSTRACT

Autoimmune disorders are increasing worldwide. Although their pathogenesis has not been elucidated yet, a complex interaction of genetic and environmental factors is involved in their onset.
Toll-like receptors (TLRs) represent a family of pattern recognition receptors involved in the recognition and in the defense of the host from invading microorganisms. They sense a wide range of pathogen associated molecular patterns (PAMPs) deriving from metabolic pathways selective of bacterial, viral, fungal and protozoan microorganisms. TLR activation plays a critical role in the activation of the downstream signaling pathway by interacting and recruiting several adaptor molecules. Although TLRs are involved in the protection of the host, several studies suggest that, in certain conditions, they play a critical role in the pathogenesis of autoimmune diseases. We review the most recent advances showing a correlation between some single nucleotide polymorphisms or copy number variations in TLR genes or in adaptor molecules involved in TLR signaling and the onset of several autoimmune conditions, such as Type I diabetes, autoimmune polyendocrinopathy candidiasis-ectodermal dystrophy, rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis. In light of the foregoing we finally propose that molecules involved in TLR pathway may represent the targets for novel therapeutic treatments in order to stop autoimmune processes.

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1. Toll-like receptors

TLRs represent a family of pattern recognition receptors [1] which are type I integral trans-membrane glycoproteins [2,3]. They show a trimodular structure [3], with an extracellular N-terminal domain and an intracellular C-terminal region. The first is constituted by about 16–28 leucine rich repeats (LRRs) and has the function to recognize PAMPs [3], whereas the second, also called Toll/IL-1 receptor (TIR) domain, is similar to the cytoplasmic region of the interleukin-1 receptor (IL-1R) [4–7]. TIR domain has a critical role for TLR function (*vide infra*) [3].

Toll was the first receptor identified in *Drosophila*, where it was involved in the dorsal ventral patterning in developing embryos [8]. Since the observation performed by the group of Hoffmann [9] that flies mutant for *Toll* were characterized by an increased susceptibility to fungal infections, several homologues of Toll receptor were identified in mammals and called TLRs [10].

In total 13 and 11 TLRs were identified in mice and in humans, respectively [2]. They are evolutionary conserved [1], playing an essential role in the recognition of PAMPs [2] from viruses, fungi, protozoan parasites and bacteria (*vide infra*) [2]. Different PAMPs are recognized by specific TLRs [5].

Several immune cells, including B lymphocytes, selective populations of T cells, dendritic cells (DCs) and macrophages [5,11] as well as non-immune cells such as epithelial cells and fibroblasts express TLRs [5]. TLR expression can quickly change in the presence of cytokines, pathogens and environmental factors [5].

It is possible to distinguish TLRs on the basis of their intracellular localization. TLR1, TLR2, TLR4, TLR5 and TLR6 can be observed at the cell membrane, while TLR3, TLR7, TLR8 and TLR9 into cell compartments, like endosomes. TLRs characterized by an intracellular localization recognize principally bacterial and viral nucleic acids, which are released and enter in contact with TLRs after being endocytosed and degraded in late endosomes or lysosomes [5]. It has been hypothesized that TLR intracellular presence plays an essential role for the discrimination between self-DNA and viral DNA, thus avoiding the development of autoimmune conditions (*vide infra*) [12].

After the recognition of PAMPs by TLRs, type I interferon (type I IFN), chemokines, inflammatory cytokines and co-stimulatory molecules are released by the immune system of the host [4–7]. More in detail, TIR domain plays a critical role in the activation of the downstream signaling pathway [3]. The function of TIR domain was identified in C3H/HeJ mouse strain, characterized by a point mutation which caused an amino acid change to histidine at position 712 of the cytoplasmic proline residue [13,14]. This amino acid substitution induced a dominant negative effect on the signaling mediated by TLRs [14,15]. TIR domain activates the downstream signaling pathway through the interaction and recruitment of several adaptor molecules [3] such as myeloid differentiation primary-response protein 88 (MyD88), TIR domain-containing adapter protein (TIRAP) (also defined as MyD88 adaptor-like (MAL)), TIR domain-containing adapter protein inducing IFN-β (TRIF) (also known as TICAM1) and TRIF-related adapter molecule (TRAM) (also defined as TICAM2). This recruitment occurs through TIR–TIR interactions [16]. Depending on which molecular adaptor is recruited, a different signaling pathway is activated; in fact whereas some pathways are similar among TLRs, others are specifically activated by only one TLR (*vide infra*) [17]. More in detail the recruitment of MyD88 occurs for all TLRs, except for TLR3. Both TLR3 and TLR4 promote the recruitment of TRIF adaptor; however while the first can initiate only the TRIF-dependent pathway, TLR4 can activate also a MyD88-dependent signaling [3]. The adaptor TIRAP is recruited in the signaling promoted by TLR1, TLR2, TLR4 and TLR6 allowing, through its TIR domain, the recruitment of MyD88 [3]. The fundamental role played by TIRAP in the interaction with MyD88 has been demonstrated in *TIRAP*-deficient mice which showed TLR2- and TLR4-defective signaling pathways similar to those observed in mice deficient for *MyD88*. Accordingly *MyD88/TIRAP*-deficient mice did not show any additional defect as compared with mice showing a single deficiency affecting these adaptors [17]. The TLR7/9 pathway is MyD88-dependent and does not require TIRAP [17].

2. TLR signaling mediated through the MyD88-dependent pathway

The MyD88-dependent pathway characterizes the signaling induced by all TLRs, whereas only TLR3 and TLR4 show a pathway independent from MyD88 (*vide infra*) (Fig. 1) [10,12].

MyD88 adaptor shows the presence of a death domain in the N-terminal region, whereas a TIR domain is localized in the C-terminal. MyD88 interacts with TLRs in their TIR domain and plays a critical function for the induction of inflammation by TLR signaling [10,17]. As regard it has been demonstrated that *MyD88* knockout mice did not show any response when stimulated with imidazoquinoline (a TLR7 ligand) or cytosine-guanine dinucleotides (CpG) DNA (a TLR9 ligand) [18–20], and interleukin-6 (IL-6) production after stimulation with bacterial flagellin (a TLR5 ligand) [21]. Furthermore *MyD88*-deficient mice did not show any inflammatory molecule production, the proliferation of B lymphocytes or endotoxin shock upon lipopolysaccharide (LPS) stimulation [10].

After TLR activation, MyD88 allows the recruitment of IL-1 receptor-associated kinase (IRAK) molecule to TLRs by interacting with the death domains of the two molecules [10]. Four members belonging to IRAK family have been identified (IRAK-1, IRAK-2, IRAK-4 and IRAK-M) [22]. Among these, IRAK-4 plays the most important role in the signaling pathway mediated by MyD88 (Fig. 1) [12,17]. The phosphorylation of IRAK causes its dissociation from MyD88 and the subsequent association with TRAF6, which constitutes an E3 ligase and is a member of the TRAF family [12]. TRAF6 is involved in the activation of TGF-β-activated kinase 1 (TAK1) [23] and the canonical IκB kinases (IKKs) constituted by IKKα and IKKβ. IKKs cause the phosphorylation of IκB protein and its follow-up degradation by a proteasome-dependent pathway permitting nuclear factor κB (NF-κB) translocation into the nucleus and activation (reviewed (*rev.*) *in* [17]).

MyD88 can also promote the activation of the mitogen-activated protein kinases (MAPKs) p38, extracellular signal-regulated kinase 1/2 (ERK1/2) and c-Jun N-terminal kinases (JNKs) [12,17].

As results of the activation of these TLR signaling pathways, several inflammatory cytokine genes are expressed [17]. The critical role played by MyD88 in the activation of inflammation has been demonstrated both in mice deficient for MyD88 (*vide supra*) and in the presence of a variant form of MyD88 known as MyD88s [10]. MyD88s represents a spliced variant which is characterized by the loss of the intermediate domain and thus could induce a negative regulation of the inflammatory process upon LPS stimulation [24,25].

3. MyD88-independent signaling pathway induced by TLR3 and TLR4

The stimulation of TLR3 and TLR4 can induce the activation of a MyD88-independent signaling pathway designed as TRIF-dependent pathway [12], through the association of TLR with TRIF molecule which occurs differently depending on which TLR is activated. In fact whereas TLR3 directly associates with TRIF, TLR4 needs the involvement

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