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Toll-like receptor co-receptors as master regulators of the immune response

Marco Di Gioia [a], Ivan Zanoni [a,b,*]

[a] University of Milano-Bicocca, Department of Biotechnology and Biosciences, P.zza della Scienza 2, 20126, Milan, Italy
[b] Children's Hospital Boston, Division of Gastroenterology, Harvard Medical School, 300 Longwood Ave, Enders, Boston, MA 02115, United States of America

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ABSTRACT

Pattern recognition receptors (PRRs) are generally recognized as the initiators of all immune responses. PRRs bind molecular patterns associated with microorganisms or endogenous mediators released by stressed tissues. Upon ligand binding, PRRs induce the activation of an inflammatory process that ultimately leads to pathogen clearance or restoration of tissue homeostasis. PRRs govern these processes, regulating the activation of a complex network of transcription factors able to induce the appropriate immune response to a specific ligand. Toll-like-receptors (TLRs) are the first and best characterized PRR family, and for a long period of time they were believed to be autonomous proteins able to recognize and initiate all the immune response to a given stimulus. Recently this view was challenged by the discovery that so-called TLR co-receptors, such as CD14 and CD36, not only favor TLR-dependent signaling but can also transduce their own signal in a TLR-independent manner. Here we will discuss the capacity of TLR co-receptors to bind different microbial and endogenous ligands and to integrate TLR functions inducing specific signaling modules.

1. Introduction

All metazoan organisms have evolved a conserved germ-line encoded immune arsenal to protect the individual from invasive bacteria, viruses, and eukaryotic pathogens (Beutler, 2004). In vertebrates, innate immune cells strategically distributed throughout the organism play an important role in this protection. These cells are able to detect microorganisms and initiate effector responses. Ultimately, this event leads to the activation of adaptive immune lymphocytes and the formation of memory cells (Joffre et al., 2009). The microbial recognition process is mediated by specialized receptors called pattern-recognition receptors (PRRs) that sense broad classes of microbial structures initially referred to as pathogen-associated molecular patterns (PAMPs) (Janeway, 1989) and now more generically termed microbial-associated molecular patterns (MAMPs). PRRs are present on both immune and non-immune cells and control the release of a selected repertoire of host defense factors, inducing a specific inflammatory response driven by the molecular signatures of the infectious agent.

Currently, PRRs can be classified into two main groups. The first includes transmembrane proteins, such as Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) (Takeuchi and Akira, 2010). The second group is composed of cytoplasmic proteins, such as NOD-like receptors (NLRs), Retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), pyrin and HIN domain-containing (PYHIN) family members and an increasing number of DNA-sensing molecules (Cerboni et al., 2013). Most PRRs regulate defense mechanisms by activating highly conserved transcriptional signaling pathways, such as the NF-κB and AP-1 pathways. More recently a new class of PRRs has been identified for its capacity to initiate a non-transcriptional program controlling the assembly of multiprotein complexes, termed inflammasomes, which activate inflammatory caspases necessary for the maturation of the pro-inflammatory cytokines interleukin 1β (IL-1β) and IL-18 and the induction of pyroptosis (Franchi et al., 2012).

TLRs are the best characterized class of PRRs and are essential regulators of innate immune responses (O'Neill et al., 2013). TLRs were long believed to have autonomous recognition and transcriptional signaling capacity, but increasing evidence suggests that accessory molecules are necessary for efficient ligand binding, TLR processing\folding and appropriate subcellular localization in order to trigger an adequate signaling pathway (Lee et al., 2012). Besides these non-transcriptional functions, specific

* Corresponding author at: Corresponding author. Tel.: +1 39 02 6448 3553.
E-mail addresses: ivan.zanoni@unimib.it, ivan.zanoni@childrens.harvard.edu (I. Zanoni).

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TLR-co-receptors have recently been identified for their capacity to also exert transcriptional functions (Zanoni et al., 2009, 2012a).

In this review we will focus our attention on TLR co-receptors, defined as specific accessory proteins that interact with a TLR and\or a TLR-ligand, facilitating or integrating TLR-mediated immune responses. In particular, we will describe the capacity of the co-receptors CD36 and CD14 to control the formation of specific signaling complexes. The engagement of these proteins, with the capacity to also transduce their own signals in a TLR-independent manner, results in very distinct inflammatory outcomes.

2. Main text

2.1. The Toll like receptors

Thirteen mammalian TLR paralogues have been identified (TLR1-10 in humans, TLR1-9 and TLR11-13 in mice) and most of them have been associated with the recognition of one or more MAMPs. Recent works have characterized ligands for TLR11 (Mathur et al., 2012; Yarovinsky et al., 2005), TLR12 (Andrade et al., 2013; Koblansky et al., 2013; Raetz et al., 2013) and TLR13 (Li and Chen, 2012; Oldenburg et al., 2012) that were previously unknown. At the moment, TLR10 is the only TLR orphaned of its ligand, although *L. monocytogenes* has recently been identified as a source of ligands for this receptor (Regan et al., 2013).

Other than microbial patterns, TLRs also recognize endogenous ligands released by damaged or stressed tissues, either in the absence or presence of pathogenic invasion, which constitute damage-associated molecular patterns (DAMPs) (Matzinger, 2002). TLR-mediated recognition of MAMPs and DAMPs can occur at the plasma membrane or intracellularly. TLR1, TLR2, TLR4, TLR5 and TLR6 primarily, but not exclusively, localize to the plasma membrane and bind lipid or protein structures that are expressed on the surface of pathogens or released in the extracellular space. By contrast, TLR3, TLR7, TLR8, TLR9, TLR11, TLR12 and TLR13 localize to intracellular vesicular compartments and are involved in the recognition of nucleic acids (TLR3-9 and TLR13) or microbial components (TLR11-12).

TLRs are type I transmembrane glycoproteins composed of an ectodomain that contains leucine-reach repeats (LRRs), one transmembrane domain and a cytosolic Toll-interleukin (IL)-1 receptor (TIR) domain implicated in the recruitment of different combinations of signaling adaptor molecules, such as MyD88, TIRAP, TRAM and TRIF. Through these proteins, TLRs can activate downstream kinases that stimulate transcription factors such as NF-κB, AP-1 and IRFs, thus inducing the production of pro-inflammatory cytokines and type I IFNs (Medzhitov and Horng, 2009).

The response process is initiated by the correct interaction between ligand and receptor, often assisted by membrane-bound or soluble co-receptor proteins. These molecules can: (1) catch and concentrate scattered ligands in the extracellular space and present them to TLRs; (2) define the specificity or increase the affinity of homo- or hetero- TLR dimers for a ligand; (3) deliver TLRs and their ligands to an optimal subcellular compartment for the signaling trigger; (4) bind a TLR ligand and activate transcriptional and non-transcriptional pathways in order to complete ligand-specific TLR responses.

Interestingly, several co-receptors work in a “promiscuous” manner, binding different kinds of ligands and controlling more than one TLR pathway. In addition, membrane-bound co-receptors can form dynamic heterocomplexes with TLR and non-TLR proteins, inducing the formation of functional modules that coordinate transcriptional and non-transcriptional responses, as we will describe below.

2.2. TLR-co-receptors: an overview

Here several TLR-co-receptors that play different functions integrating or favoring the signaling of the TLRs are described. Specific chapters will be dedicated to CD14 and CD36.

2.2.1. HMGB1

High-mobility group box 1 (HMGB1) is a chromatin-binding protein involved in nucleosome formation that regulates the expression of several genes by stabilizing DNA interactions with transcription factors (Bustin, 1999; Park et al., 2003; Stros et al., 2002; West et al., 2004a). HMGB1 is passively released by necrotic cells (Scaffidi et al., 2002) or actively secreted by immune cells upon pro-inflammatory stimulation (Tang et al., 2007), thus mediating cytokine-like functions. Indeed, HMGB1 is recognized as a DAMP by particular PRRs, i.e. receptor for advanced glycation end products (RAGE) (Kokkola et al., 2005; Taguchi et al., 2000), TLR2, TLR4 (Park et al., 2004, 2006) and CD14 (Kim et al., 2013). However, HMGB1 has also been described as a co-receptor of TLR9, since it is able to bind CpG DNA, transport it in endosomal compartments in a RAGE-dependent way and interact with TLR9 (Ivanov et al., 2007; Tian et al., 2007). Recently, it has been proposed that HMGB1 and closely related proteins may function as nonspecific universal sentinels for nucleic acids and as co-receptors for more discriminative PRRs, such as TLR3, TLR7 and TLR9 (Yanai et al., 2009).

2.2.2. LL-37

LL-37 is an amphipathic peptide with bactericidal activity (Travis et al., 2000) released by macrophages, neutrophils and several types of epithelial-associated cells as a consequence of TLR engagement and vitamin D exposure (Liu et al., 2006). LL-37 is also rapidly induced upon skin injury (Gregorio et al., 2010) and is expressed at high levels in keratinocytes of psoriasis patients (Ong et al., 2002). In this context, LL-37 forms stable complexes with self-DNA that trigger type I IFN production via endosomal TLR9 in plasmacytoid dendritic cells (DCs) (Lande et al., 2007) and orchestrate autoimmune pathology. It has been determined that LL-37 binds DNA dense structures that are resistant to extracellular enzymatic degradation (Lande et al., 2007). The complex is then internalized in a receptor-independent lipid raft-mediated endocytotic process (Sandgren et al., 2004) and presented to TLR9. In monocytes, LL37-DNA complexes can escape from endosomal compartments and reach the cytosol, where they can activate nucleic acid sensors and induce a TLR-independent STING-TABK1-dependent induction of type I IFNs (Chamilos et al., 2012). LL-37 has also been shown to bind self-RNA and to work as a co-receptor for TLR3 (Lai et al., 2011), TLR7 and TLR8 (Ganguly et al., 2009).

2.2.3. LBP

LPS-binding protein (LBP) is a class I acute phase protein secreted into the bloodstream mainly by hepatocytes (Schumann et al., 1996). Recently, the first crystal structure of LPB has been resolved and it has been shown how its conformational modifications might increase the severity of bacterial infections (Eckert et al., 2013). Indeed, LBP is implicated in the recognition of lipopolysaccharide (LPS) derived from the outer membrane of gram-negative bacteria (Mathison et al., 1992). This interaction results in LPS multimer disaggregation, enabling LPS presentation to CD14 and then to TLR4 (Tsukamoto et al., 2010). In addition, LBP interacts with other bacterial components such as peptidoglycan, lipoteichoic acid (LTA) and lipoproteins, being also a TLR1, TLR2