

Pathogen Strategies to Evade Innate Immune Response: A Signaling Point of View

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1. Introduction

An effective host defense against pathogens requires appropriate recognition of the invading microorganism by immune cells, conducting to an inflammatory process that involves recruitment of leukocytes to the site of infection, activation of antimicrobial effector mechanisms and induction of an adaptive immune response that ultimately will promote the clearance of infection. All these events require the coordination of multiple signaling pathways, initially triggered by the contact of the pathogen with innate immune cells. The “signal alarm” is normally triggered by ligation of microorganism, or microorganism’s components, to pattern-recognition receptors, causing their phosphorylation and recruitment of adapter molecules, which in turn will activate second messengers within the cytosol of the cells, allowing the transduction of the signal. The second messengers are often protein kinases that in a cascade process ultimately activate the transcription factors responsible for the expression of effector molecules like, cytokines, chemokines and reactive oxygen species, crucial elements to mount an adequate immune response. The activity of such critical intracellular signaling pathways is a process extremely well controlled by a balance of positive and negative regulation, being the activation of a given protein kinase normally counterbalanced by the activation of its opposing phosphatase. However, as part of their pathogenic strategies, several microorganisms exploit host cell signaling mechanisms by distorting this balance between positive and negative signals. They hijack crucial immune-cell signaling pathways, subverting the immunogenic abilities of these cells and evading this way the host immune response. In the last few years a great effort has gone into understanding the molecular mechanisms behind this subversion, and various signaling cascades were identified as main targets of pathogens and virulence factors. Among these targets, assume particular importance the transcription factor nuclear factor- κ B (NF- κ B), a cornerstone of innate immunity and inflammatory responses, as well as the mitogen activated protein kinases (MAPKs), signaling cascades implicated in the regulation of crucial aspects of immunity. Overall in this chapter, we will provide an overview of the current understanding of how pathogens interact with host cells and how these microorganisms exploit host immune response in a signaling point of view.

2. Immune response to invading microorganisms

In mammals, immune system can be subdivided into two branches: innate and adaptive immunity. Following infection, innate immune cells like macrophages, dendritic cells (DCs) and neutrophils (collectively called phagocytes) engulf and destroy microorganisms, representing that way a rapid first defense barrier against infection. In turn, adaptive immunity is mediated via the generation of antigen-specific B and T lymphocytes, through a process of gene rearrangement resulting in the production and development of specific antibodies and killer T cell, respectively. Adaptive immunity is also behind immunological memory, allowing the host to rapidly respond when exposed again to the same pathogen. Contrarily to the originally thought, the innate immune response is not completely nonspecific, but rather is able to discriminate between self antigens and a variety of pathogens (Akira et al., 2006). Furthermore, much evidence has demonstrated that pathogen-specific innate immune recognition is a prerequisite to the induction of antigen-specific adaptive immune responses (Hoebe et al., 2004; Iwasaki & Medzhitov, 2010), being dendritic cells central players in this linking (Steinman, 2006). DCs are specialized antigen-presenting cells that function as sentinels, scanning changes in their local microenvironment and transferring the information to the cells of the adaptive immune system (Banchereau & Steinman, 1998; Banchereau et al., 2000). Upon activation by microorganisms or microorganism components, immature DCs suffer a complex process of morphological, phenotypical and functional modifications to become mature DCs that enter draining lymphatic vessels and migrate to the T-cell zones of draining lymph nodes where they present antigens to T lymphocytes. Depending on their maturation/activation profile, DCs

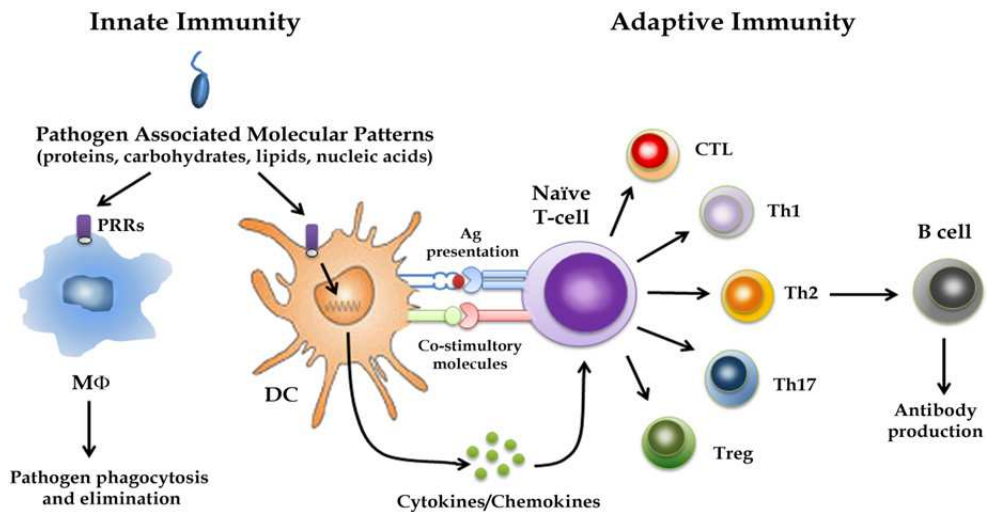


Fig. 1. Dendritic cells link innate to adaptive immunity. Once in contact with microbial antigens, DCs mature and migrate to draining lymph nodes where they present antigens to naïve T lymphocytes. Different pathogens trigger distinct DCs maturation profiles, leading to the polarization of different T-cell subsets. The adaptive immune response is therefore modulated, in some extent, to match the nature of the pathogen. Ag: antigen; CTL: cytotoxic T cell; DC: dendritic cell; Mφ: macrophage.

will polarize and expand distinct T-cell subsets (T-helper cells [Th1, Th2, and Th17], regulatory T cells, and cytotoxic T cells) (Sporri & Reis e Sousa, 2005; Diebold, 2009) and given that the recognition of different microorganisms lead to distinct DC maturation/activation profiles, the adaptive immune response is, therefore, modulated to match the nature of the pathogen (Figure 1)

2.1 Recognition of microorganisms by innate immune cells

To a rational understanding of molecular mechanisms by which pathogens escape the immune system, we need first to know how our immune cells sense microorganisms and spread the “alarm”.

Innate immune cells, like macrophages and DCs, recognize microorganisms through sensing conserved microbial components, globally designated as pathogen associated molecular patterns (PAMPs) (Kawai & Akira, 2010; Takeuchi & Akira, 2010; Medzhitov, 2007). These molecular patterns are normally essential components of microbial metabolism, including proteins, lipids, carbohydrates and nucleic acids, not subjected to antigenic variability. Another important feature of PAMPs is that they are markedly distinct from self-antigens, allowing the innate immune system to discriminate between self and non-self.

The recognition of PAMPs is mediated by constitutively expressed host’s germline-encoded pattern-recognition receptors (PRRs), such as Toll-like receptors (TLRs), C-type lectin receptors (CLRs), retinoic acid-inducible gene-1(RIG-1)-like receptors and nucleotide-oligomerization domain (NOD)-like receptors. The beauty of this evolutionary sensor mechanism is that different PRRs react with specific PAMPs, triggering a signaling pathway profile that ultimately lead to distinct anti-pathogen responses (Akira, 2009). Therefore, innate immunity is a key element in the infection-induced non specific inflammatory response as well as in the conditioning of the specific adaptive immunity to the invading pathogens (Akira et al., 2001; Iwasaki & Medzhitov, 2004).

2.1.1 Toll-like receptors

Among PRRs, TLRs are by far the most intensively studied and the more expressive group, being considered the primary sensors of pathogen components. TLRs are type I membrane glycoproteins formed by extracellular leucine rich repeats involved in PAMP recognition, and a cytoplasmic signaling domain homologous to that of the interleukin 1 receptor (IL-1R), know as Toll/IL-1R homology (TIR) domain. These receptors were originally identified in *Drosophila* as essential elements for the establishment of the dorso-ventral pattern in developing embryos (Hashimoto et al., 1988). However, in 1996, Hoffmann and colleagues would initiate a novel era in our understanding of innate immunity, demonstrating that Toll-mutant flies were highly susceptible to fungal infection, showing that way that TLRs were involved in the defense against invading microorganisms (Lemaitre et al., 1996). Afterward, mammalian homologues of Toll receptor were progressively identified, and actually most mammalian species are believed to have between ten and thirteen types of TLRs. In human, ten functional receptors (TLR1-10) have been identified so far and an

TLR family	Cellular location	Microbial components	Pathogens
TLR1/2	Cell surface	Tri-acyl lipopeptides Soluble factors	Bacteria, mycobacteria <i>Neisseria meningitides</i>
TLR2	Cell surface	Diacyl lipopeptides Triacyl lipopeptides Peptidoglycan Lipoteichoic acid Porins Lipoarabinomannan Phenol-soluble modulin tGPI-mutin Glycolipids Hemagglutinin protein Zymosan Phospholipomannan Glucuronoxylomannan	Mycoplasma Bacteria and mycobacteria Gram-positive bacteria Gram-positive bacteria <i>Neisseria</i> Mycobacteria <i>Staphylococcus epidermidis</i> <i>Trypanosoma Cruzi</i> <i>Treponema maltophilum</i> Measles virus Fungi <i>Candida albicans</i> <i>Cryptococcus neoformans</i>
TLR3	Endolysosome	Viral double-stranded RNA	Vesicular stomatitis virus, lymphocytic choriomeningitis virus reovirus
TLR4	Cell surface	LPS Fusion protein Envelope proteins HSP60 Manan Glycoinositolphospholipids	Gram-negative bacteria Respiratory syncytial virus Mouse mammary tumor virus <i>Chlamydia pneumoniae</i> <i>Candida albicans</i> <i>Trypanosoma</i>
TLR5	Cell surface	Flagellin	Flagellated bacteria
TLR6/2	Cell surface	Diacyl lipopeptides Lipoteichoic acid Zymosan	Mycoplasma Group B Streptococcus <i>Saccharomyces cerevisiae</i>
TLR7	Endolysosome	Viral single-stranded RNA RNA	Several virus Bacteria from group B <i>Streptococcus</i>

TLR family	Cellular location	Microbial components	Pathogens
TLR8 (only human)	Endolysosome	Viral single-stranded RNA	Several virus
TLR9	Endolysosome	CpG-DNA dsDNA viruses Hemozoin	Bacteria and mycobacteria Herpes simplex virus and murine Cytomegalovirus Plasmodium
TLR10	Cell surface	Unknown	Unknown
TLR11 (only mouse)	Endosome	Profilin-like molecule	<i>Toxoplasma gondii</i> Uropathogenic <i>E. coli</i>
TLR12 (only mouse)	Cell surface	ND	Unknown
TLR13 (only mouse)	Cell surface	ND	Virus

Table 1. Toll-like receptors cellular location and microbial ligands. ND: not determined.

eleventh has been found to be encoded at gene level but, as it contains several stop codons, protein is not expressed (Zhang et al., 2004). TLRs are involved in sensing a wide panel of microbial products (Kawai & Akira, 2010), including lipids, peptidoglycans, proteins, and nucleic acids (Table 1). Regarding their cellular location, these receptors are either found at cell surface membrane or within intracellular compartments. A growing body of data suggests that TLRs involved in sensing bacterial chemical structures (TLR1, TLR2, TLR4 and TLR5) are located on the cell surface, while nucleic acid-recognizing TLRs (TLR3, TLR7, TLR8 and TLR9) are uniquely positioned intracellularly (McGettrick & O'Neill, ; Barton & Kagan, 2009).

2.1.1.1 Signaling through TLRs

Recognition of microbial components by TLRs leads to the activation of an intricate network of intracellular signaling pathways that ultimately result in the induction of molecules crucial to the resolution of infection such, proinflammatory cytokines, type I interferon (IFN), chemokines, and co-stimulatory molecules (Takeuchi & Akira, 2010 ; Kumar et al., 2010). These signaling cascades originate from cytoplasmic TIR domains and are mediated via the recruitment of different TIR domain-containing adaptor molecules, such as myeloid differentiation primary response gene 88 (MyD88), TIR-containing adaptor protein/MyD88-adaptor-like (TIRAP/MAL), TIR-containing adaptor inducing interferon- β (IFN- β)/TIR-domain-containing adaptor molecule 1 (TRIF/TICAM1) and TIR-domain-containing adaptor molecule/TRIF-related adaptor molecule 2 (TRAM/TICAM2) (Fitzgerald et al.,

2001; Horng et al., 2001; Yamamoto et al., 2002; Takeda & Akira, 2004; Yamamoto et al., 2004).

In the signaling pathways downstream of the TIR domain, the TIR domain-containing adaptor MyD88 assumes a crucial role. With exception for TLR3, all TLRs recruit MyD88 and initiate MyD88-dependent signaling cascades to activate NF- κ B and MAP kinases. MyD88 is used as the sole adaptor in TLR5, TLR7 and TLR9 signaling, while TLR1, TLR2, and TLR6, additionally recruit the adaptor TIRAP. TLR4 uses the four adaptors, including MyD88, TIRAP, TRIF and TRAM (Yamamoto et al., 2002; Yamamoto et al., 2003)

In a general point of view, TLR signaling could be divided into two major pathways: MyD88-dependent and TRIF-dependent pathways.

MyD88-dependent pathway

Following stimulation, MyD88 recruits IL-1 receptor-associated kinase proteins (IRAK) to TLRs, resulting in IRAK phosphorylation and subsequent association and activation of tumor necrosis factor receptor (TNFR)-associated factor 6 (TRAF6) (Swantek et al., 2000; Suzuki et al., 2002). The IRAK-1/TRAF6 complex dissociates from the TLR receptor and associates with TGF- β -activated kinase 1 (TAK1) and TAK1 binding proteins, TAB1 and TAB2. From this new formed complex, IRAK-1 is degraded, whereas the remaining complex of TRAF6, TAK1, TAB1, and TAB2 is transported across the cytosol where it forms large complexes with E2 protein ligases such as the Ubc13 and Uev1A. As result, TRAF6 is polyubiquitinated and thereby induces TAK1 activation (Deng et al., 2000) which, in turn, activates the I κ B kinases complex (IKK). The active IKK complex promotes the phosphorylation and subsequent ubiquitination of the NF- κ B inhibitory protein I κ B- α , leading to its proteosomal degradation. This allows the NF- κ B subunits to be translocated to the nucleus, where they initiate the transcription of genes involved in inflammatory response (Wang et al., 2001). Additionally to NF- κ B activation, MyD88-dependent signaling cascade also culminates into the activation of the three MAPK pathways (extracellular signal-regulated kinase (ERK), Jun N-terminal kinase (JNK) and p38), regulating both, the transcription of inflammatory genes and the mRNA stability of those transcripts (Figure 2).

TRIF-dependent pathway

Besides this MyD88-dependent pathway, NF- κ B could also be activated follow TLR3 and TLR4 engagement in a TRIF-dependent manner. In TLR3 signaling, TRIF interacts directly with the TIR domain of the receptor, whereas for TLR4 another TIR domain containing adaptor, TRAM/TICAM-2, acts as a bridging between TLR4 and TRIF (Oshiumi et al., 2003; Oshiumi et al., 2003). In this pathway, TRIF recruits TRAF-6 and RIP1, molecules that cooperate in TAK1 activation, and lead to robust NF- κ B activation.

TRIF-dependent signaling cascade also assumes a crucial role in the expression of type I IFN and IFN-inducible genes (ISGs). These genes are mainly potent antiviral molecules and their expression, follow TLR3 sensing of viral double stranded RNA, is of critical importance for the control of viral infections (review by Taniguchi et al., 2001). In this pathway, TRIF associates with TBK1 and IKKi, which in turn phosphorylate IRF3 and IRF7, leading to their nuclear translocation and induction of type I IFN genes and co-stimulatory molecules (Figure 2).

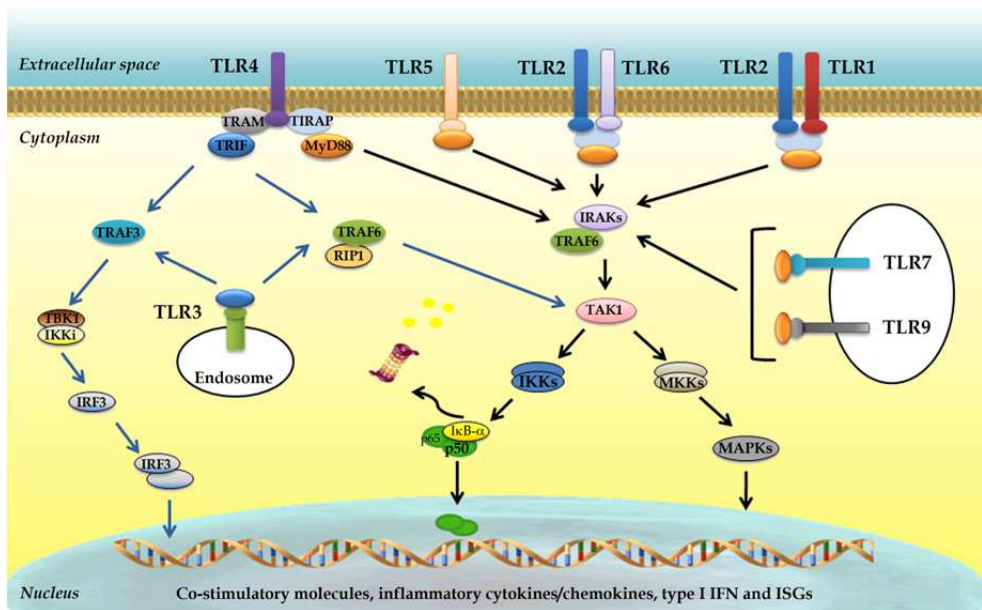


Fig. 2. Schematic representation of TLRs-mediated signaling. TLR signaling pathways were triggered by recognition of PAMPs by plasma membrane-localized TLRs, such as TLR4, TLR5, and TLR2 (TLR1 and TLR6 form heterodimers with TLR2 becoming functional receptor complexes) and endosomal-localized TLRs, such as TLR3, TLR7, and TLR9. Depending on the adaptor molecules involved, two major pathways could be established: the MyD88-dependent pathway (black arrows) and the TRIF-dependent pathway (blue arrows). MyD88-dependent signaling is initiated through the recruitment and activation of IRAK that associates and activates TRAF6. The IRAK-1/TRAF6 complex subsequently activates the TAK1 kinase, which in turn activates the IKK complex. The active IKK complex activates NF- κ B subunits leading to their translocation to nucleus where they initiate the transcription of inflammatory cytokines/chemokines genes. In the TRIF-dependent signaling pathway, TRIF recruits TRAF-6 and RIP1, molecules that cooperate in TAK1 activation, leading to NF- κ B activation. Besides, TRIF also recruits TBK1 and IKKi, leading to phosphorylation and nuclear translocation of IRF3 and IRF7, which results in transcription of type I IFN genes and co-stimulatory molecules

2.1.2 C-Type lectin receptors

C-type lectin receptors are a large superfamily of proteins characterized by the presence of one or more C-type lectin-like domains (CTLDs) that were originally described as Ca^{2+} -dependent, carbohydrate binding proteins (Weis et al., 1998). Over the past decade more than 60 CLR have been identified in human immune cells (van Vliet et al., 2008). In recent years, some of these CLR have emerged as PRRs with important roles in the induction of immune responses against numerous pathogens. Although the TLRs have a well defined role in alerting innate immune cells to the presence of pathogens, CLR are mainly involved in the recognition and subsequent endocytosis or phagocytosis of microorganisms. These

receptors have also crucial functions in recognizing glycan structures expressed by the host, facilitating this way cellular interaction between DCs and other immune cells, like T-cells and neutrophils (Geijtenbeek et al., 2000; van Gisbergen et al., 2005; Bogoevska et al., 2006).

Based on their structural features, C-type lectin receptors are sorted into two major groups: type I and type II receptors. Type I receptors are transmembrane proteins with multiple carbohydrate recognition domains (CRDs), being members of this group the mannose receptor (MR), DEC-205 (CD205), and Endo 180 (CD280), among others. Type II receptors are also transmembrane proteins, but in contrast, they have just a single CRD. DC-specific intercellular adhesion molecule (ICAM)-3 grabbing nonintegrin (DC-SIGN), Langerin, DC-associated C-type lectin-1 (Dectin 1), Dectin 2, DC-immunoreceptor (DCIR) and macrophage-inducible C-type lectin (Mincle) are examples of type II CLRs.

Originally, CLRs were thought to be predominantly involved in antifungal immunity, but are currently recognized to participate in immune responses induced by a wide spectrum of other pathogens, including bacteria, viruses and nematodes (Table 2).

2.1.2.1- Signaling through C-Type lectin receptors

Besides its roles in recognition and uptake of antigens, CLRs have also important signaling functions, shaping the immune responses to innumerable pathogens. Whereas some CLRs possess intrinsic signaling properties and are thus capable of directly activate transcription factors leading to cytokines expression, others predominantly act as modulators of responses to other PRRs, such as TLRs. This crosstalk between groups of PRRs is actually seen as a crucial event by which immune responses are balanced through collaborative induction of positive or negative feedback mechanisms. While TLRs engagement triggers

CLR Group	CLR	Microbial components	Pathogens
Type I	Mannose receptor (CD206)	High-mannose oligosaccharides, Fucose, Sulphated sugars and N-Acetylgalactosamine	<i>M. tuberculosis</i> <i>M. kansasii</i> <i>Francisella tularensis</i> , <i>Klebsiella pneumoniae</i> , HIV-1 and Dengue virus <i>Candida albicans</i> <i>Cryptococcus neoformans</i> <i>Pneumocystis carinii</i> <i>Leishmania spp.</i>
	DEC205 (CD205)	ND	ND
Type II	DC-SIGN (CD209)	High-mannose oligosaccharides and fucose	<i>M. tuberculosis</i> , <i>M.leprae</i> BCG, <i>Lactobacilli</i> spp. <i>Helicobacter pylori</i> HIV-1 and Dengue virus <i>Schistosoma mansoni</i>

			<i>Leishmania spp.</i> <i>Candida albicans</i> <i>Ixodes scapularis</i> Salp15 protein
Langerin (CD207)	High-mannose oligosaccharides, Fucose and N-Acetylgalactosamine		HIV-1 <i>M.leprae</i>
CLEC5A	ND		Dengue virus
MGL (CD301)	Terminal N- Acetylgalactosamine		<i>Schistosoma mansoni</i> Filoviruses
Dectin 1 (CLEC7A)	β -1,3 glucans		<i>Pneumocystis carinii</i> <i>Candida albicans</i> <i>M. tuberculosis</i> <i>Aspergillus fumigatus</i> <i>Histoplasma</i> <i>capsulatum</i>
CLEC2 (CLEC1B)	ND		HIV-1
MICL (CLEC12A)	ND		ND
CLEC12B	ND		ND
DNGR1 (CLEC9A)	ND		ND
Dectin 2 (CLEC6A)	High-mannose oligosaccharides		<i>Aspergillus fumigatus</i> <i>M. tuberculosis</i> <i>Candida albicans</i> <i>Trichophyton rubrum</i> <i>Paracoccoides</i> <i>brasiliensis</i> Soluble components of <i>Schistosoma mansoni</i> eggs
Mincle (CLEC4E)	α -mannose Trehalose-6,6-dimycolate		<i>Malassezia spp</i> Mycobacteria.
BDCA2 (CD303)	ND		ND
DCIR (CLEC4A)	ND		HIV-1

Table 2. Major C-type lectin receptors involved in pathogen recognition. BCG: Bacillus Calmette-Guérin; HIV-1: Human immunodeficiency virus type 1; ND: not determined.

intracellular signaling cascades that result in macrophage activation, DC maturation and ultimately T cell activation, binding of ligands to CLR normally results in tolerogenic signals. Therefore the cross talk between TLRs and CLR may fine-tune the balance between immune activation and tolerance. In terms of immunity this represents a paradox: if crucial to maintain tolerance to self-antigens, CLR could be used by pathogens to escape immune system. Several pathogens exploit this "security breach", taking part of their capacity to activate C-type lectin receptors to promote an unresponsive state against their antigens recognized by other PPRs and increasing, this way, their chances of survival in host.

2.1.2.1.1 Mannose receptor

The mannose receptor is a type I transmembrane protein expressed on the surface of macrophages and immature dendritic cells. This receptor is primarily involved in recognition, phagocytosis and processing of glycans structures containing mannose, fucose and N-acetylglucosamine, molecules commonly found on the cell walls of pathogenic microorganisms, such as mycobacteria, fungus, parasites and yeast (East & Isacke, 2002).

While MR has been shown to be involved in the expression of several pro and anti-inflammatory cytokines, the lack of an intracellular signaling motif on its cytoplasmic tail indicates that it requires an interaction with other PPRs in order to trigger any signaling cascade (Gazi & Martinez-Pomares, 2009). In fact, it was recently showed an intriguing interplay between the mannose receptor and another main CLR, Dectin-1. The recognition of fungi species, like *Candida albicans*, *Aspergillus fumigates* and *Pneumocystis carinii* by Dectin-1 enhances MR shedding in a serine/threonine protein kinase Raf-1 and phosphatidylinositol 3-kinase (PI3K)-dependent pathways. As these cleaved MR-cysteine-rich domains are capable of binding fungi particles and are recognized by tissues lacking mannose receptors this could represent a system delivery of MR-ligands to organs that do not possess MR receptors.

2.1.2.1.2 DC-SIGN

DC-SIGN is one of the most extensively studied type II CLR. This receptor is primarily expressed in myeloid DCs being involved in numerous functions, like egress of DC-precursors from blood to tissues, DC-T-cell interactions and antigen recognition (Geijtenbeek et al., 2000; van Kooyk & Geijtenbeek, 2003). The receptor is involved in recognition of carbohydrate antigens of viruses, bacteria and protozoa, modulating the TLR signaling triggered by these pathogens.

Binding of several pathogens, including *M. tuberculosis*, *C. albicans* and HIV-1, to DC-SIGN triggers three routes that converge to activate Raf-1: the activation of the small GTPase Ras protein leads to its association with Raf-1 allowing Raf-1 phosphorylation at residues Ser338, Tyr340 and Tyr341, by p21-activated kinases (PAKs) and Src kinases, respectively. Raf-1 activation leads in turn to the modulation of TLR-induced NF- κ B activation. After TLR-induced nuclear translocation of NF- κ B, activated Raf-1 mediates the phosphorylation of NF- κ B subunit p65 at the Ser276, which in turn leads to p65 acetylation. Acetylated p65 prolongs and increases the transcription of *IL-10* gene resulting in an augmented production of the immunosuppressive cytokine IL-10 (Gringhuis et al., 2007) (Figure 3a).

Recently, a different mechanism of TLR modulation by DC-SIGN was described after the interaction of the receptor with Salp15, an immunosuppressive protein of tick saliva (Hovius et al., 2008). Binding of Salp15, from the tick *Ixodes scapularis*, to DC-SIGN activates RAF1 that, with another not yet defined receptor, leads to MAPK/ERK kinase (MEK) activation. MEK-dependent signaling attenuates, in turn, the TLR-induced proinflammatory cytokine production at two distinct levels: enhancing the decay of *Il6* and *Tnf* (tumor necrosis factor) mRNA and decreasing nucleosome remodeling at the *IL-12p35* promoter, resulting in impaired IL-12p70 cytokine production (Figure 3b).

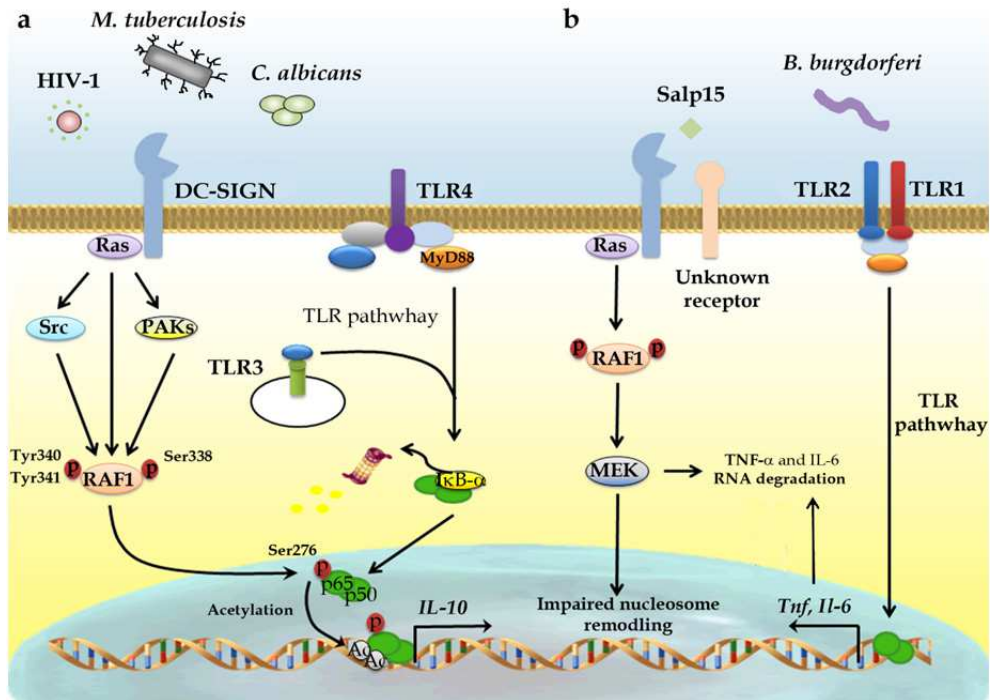


Fig. 3. Signaling through DC-SIGN. a) Carbohydrate antigens of HIV-1, *Mycobacterium tuberculosis* and *Candida albicans* are recognized by DC-SIGN, leading to activation of the small GTPase Ras proteins which associate with the serine/threonine protein kinase RAF1. RAF1 is then phosphorylated at residues Ser338, and Tyr340 and Tyr341 by PAKs and Src kinases, respectively. RAF1 activation leads to modulation of TLR-induced NF-κB activation by inducing the phosphorylation of p65 at Ser276 and its subsequent acetylation (Ac). Acetylated p65 exhibits enhanced transcriptional activity, particularly for *IL-10* gene, thereby increasing the production of IL-10. b) Binding of the salivary protein Salp15 from the tick *Ixodes scapularis* to DC-SIGN activates RAF1, and by a yet unknown co-receptor, changes downstream effectors of RAF1, leading to MEK activation. MEK-dependent signaling modulates *B. burgdorferi*-induced TLR1-TLR2-dependent pro-inflammatory cytokine production by enhancing the decay of *Il-6* and *Tnf* mRNA.

2.1.2.1.3 Dectin 1

In humans, Dectin-1 is mainly expressed in myeloid cells, such as macrophages, neutrophils and dendritic cells (Taylor et al., 2002), although it was also been found in other cell types, like B-cells, eosinophiles and mast cells (Ahren et al., 2003; Olynych et al., 2006). Unlike many other CLR, Dectin-1 recognizes β -glucans in a Ca^{2+} -independent fashion (Brown & Gordon, 2001) and it lacks the conserved residues within its CRD that are typically necessary for binding carbohydrate ligands (Weis et al., 1998). The receptor contains a single CRD in the extracellular region and an immunoreceptor tyrosine-based activation (ITAM)-like motif within its intracellular tail.

It was the first non-TLR PPR shown to possess intrinsic signaling properties, being able to signal through both, spleen tyrosine kinase (Syk)-dependent and Syk-independent pathways (Brown, 2006) (Figure 4).

In the Syk-dependent pathway, and upon binding to Dectin-1, the ITAM-like motif is phosphorylated in tyrosine residues via Src kinases, promoting the recruitment of the signaling protein Syk (Rogers et al., 2005). Activated Syk then signals through the downstream transducer caspase recruitment domain protein (Card)9, that forms a complex with the B cell lymphoma 10 (Bcl10) and the mucosa associated lymphoid tissue translocation protein 1 (Malt1) (Gross et al., 2006). This activated CARD9-BCL10-MALT1 (CBM) complex controls NF- κ B activation and subsequent expression of cytokines/chemokines, like TNF- α , IL-1 β , IL-10, IL-6, IL-23, CCL2 and CCL3 (LeibundGut-Landmann et al., 2007). Dendritic cells, through this Dectin-1-Syk-Card9 axis and by orchestration of the cytokines IL-1 β , IL-6 and IL-23, promote the differentiation of Th17 helper cells, establishing this way a crucial host response against extracellular bacteria and fungi (Osorio et al., 2008). Moreover, there are evidences of a collaborative Dectin-1/TLR2 pathway for the induction of a specific *Candida albicans*-Th17 response, by the induction of prostaglandin E2, which in turn up-regulates the Th17 polarizing cytokines IL-6 and IL-23 (Smeekens et al., 2010). Besides the canonical NF- κ B activation, Dectin-1 can also activate, through Syk, the NIK-dependent non-canonical RelB subunit of NF- κ B (Gringhuis et al., 2009). Another Syk downstream signal recently described, points to the activation of phospholipase C gamma-2, which in turn activates several calcium-dependent and MAPKs-dependent pathways (Xu et al., 2009). One of these calcium-mediated responses involves the calcineurin activation of the nuclear factor of activated T-cells (NFAT), leading to the expression of the cytokines IL-2 and IL-10 and of inflammatory mediators, like cyclooxygenase-2 (COX-2) (Suram et al., 2006; Goodridge et al., 2007). Recently, another calcium-dependent pathway downstream of Dectin-1 and Syk was described. In this pathway, activated calmodulin-dependent kinase II and Pyk2 promote the activation of the ERK-MAPK pathway and CREB, resulting in the generation of an oxidative burst and in the production of IL-2 and IL-10 (Slack et al., 2007; Kelly et al., 2010). The generated reactive oxygen species act through NLRP3 inflammasome and are essential to IL-1 β production in response to fungal infections (Gross et al., 2009; Kumar et al., 2009; Said-Sadier et al., 2010).

The Syk-independent pathway downstream Dectin-1 is not fully characterized; however, recent findings suggest that Dectin 1 activation leads to the phosphorylation and activation of RAF1 by Ras proteins, which promotes the phosphorylation of p65, at Ser276 residue, facilitating its acetylation by the histone acetyltransferases CREB-binding protein. Similarly to that described for DC-SIGN, acetylated p65 prolongs and increases the transcription of *IL-10* gene.

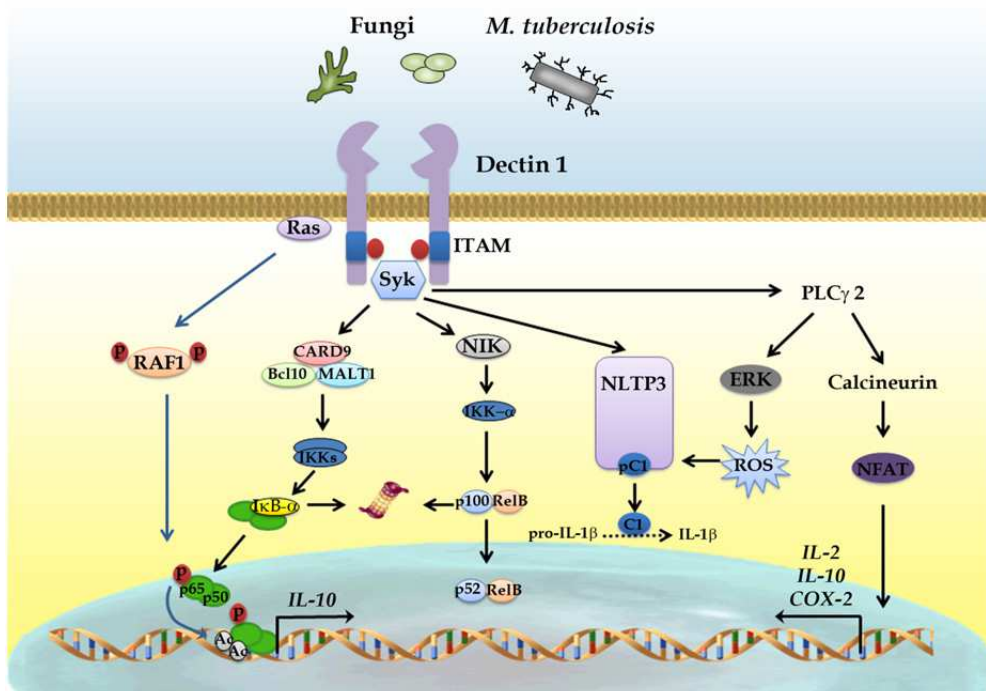


Fig. 4. Signaling through Dectin 1. Recognition of microorganisms by Dectin 1 leads to signal through both, Syk-dependent (black arrows) and Syk-independent pathways (blue arrows). In the Syk-dependent pathway, binding of glucans to Dectin-1 causes the phosphorylation of ITAM-like motifs in its tyrosine residues. Syk is then recruited to the two phosphorylated receptors, leading to the formation of a complex involving CARD9, BCL-10 and MALT1. This activated complex controls NF- κ B activation and subsequent expression of cytokines/chemokines, like TNF- α , IL-1 β , IL-10, and IL-6. Activation of Syk also leads to the activation of the non-canonical NF- κ B pathway, a process mediated by NIK and IKK, and in which RelB-p52 dimers were translocated to nucleus. Another Syk downstream signal leads to activation of PLC γ 2, which in turn activates MAPKs-dependent and calcineurin-dependent pathways. Activation of calcineurin promotes the activation of NFAT, leading to the expression of the cytokines IL-2 and IL-10 and COX-2. In turn, activation of ERK, results in the generation of an oxidative burst that acting through the NLRP3 inflammasome, is essential to IL-1 β production. In the Syk-independent pathway, Dectin 1 activation leads to the phosphorylation and activation of RAF1 by Ras proteins, leading in turn to the phosphorylation and acetylation of p65. Binding of acetylated p65 to the *IL-10* enhancer, increases the transcription of the gene. C1: caspase 1; pC1: pro-caspase.

2.1.2.1.4 Dectin 2

Dectin 2 was originally found in DCs (Ariizumi et al., 2000), although it is also expressed in tissue macrophages, inflammatory monocytes, B cells, and neutrophils (Fernandes et al., 1999). The receptor has been shown to be involved in recognition of mannan-like or

mannan-containing glycoproteins, glycolipids or oligomannosides present in fungi hyphae, being critical for the establishment of Th17 antifungal responses (Sato et al., 2006; Robinson et al., 2009). Furthermore, murine Dectin-2 was also associated with helminth infections by recognition of soluble components derived from the eggs of *Schistosoma mansoni* (Ritter et al., 2010). In contrast to Dectin-1, Dectin-2 does not contain defined signaling motifs in its cytoplasmic tail and is therefore incapable of inducing intracellular signaling on its own. However, the receptor associates with the adaptor molecule Fc receptor γ chain (FcR γ) to transduce intracellular signals, through a Dectin 2-FcR γ -Syk-dependent pathway. FcR γ chain contains an ITAM motif that is dually phosphorylated by Src kinases, promoting the recruitment and activation of Syk. Syk activates, in turn, the NF- κ B and MAPKs pathways in a CARD9-dependent or independent fashion, respectively (Saijo et al., 2010) (Figure 5a).

2.1.2.1.5 Mincle

Mincle is a type II transmembrane protein with a highly conserved C-type lectin domain, predominantly expressed in macrophages. It has been implicated in the recognition of *Saccharomyces cerevisiae*, *C. albicans* and mycobacteria, and was shown to be responsible for specific recognition of α -mannose residues in *Malassezia* species (Bugarcic et al., 2008; Wells et al., 2008; Ishikawa et al., 2009; Yamasaki et al., 2009). Similarly to Dectin-2, it lacks a signaling motif but couples to FcR γ to transduce intracellular signals. Ligation to Mincle of trehalose-6,6-dimycolate, an abundant mycobacterial cell wall glycolipid, was shown to trigger a FcR γ -Syk-CARD9 dependent pathway, leading to protective Th1 and Th17 immune responses (Werninghaus et al., 2009) (Figure 5b).

2.1.2.1.6 BDCA2

BDCA2 is a type II C-type lectin receptor primarily expressed in human plasmacytoid dendritic cells (Dzionic et al., 2001). As endogenous or microbial ligands for BDCA2 have not yet been identified, it is difficult to understand the pathophysiological implications of this CLR. However, it has been shown, by treatment with anti-BDCA-2 monoclonal antibodies, that the receptor crosstalk with other PPARs, namely TLR-9, decreasing the induced IFN-I expression (Jahn et al., 2010). As for Dectin-2 and Mincle, BDCA2 signals through the ITAM motifs of the FcR γ chain. Activation of BDCA2 results in phosphorylation of ITAM motifs of FcR γ , followed by the recruitment and activation of Syk. Activated Syk leads to the formation of a complex, consisting of B cell linker (BLNK), Bruton's tyrosine kinase (BTK) and phospholipase C2 (PLC2), which induces calcium mobilization. This calcium increase appears to be involved in the inhibition of MYD88 adapter recruitment to TLR9 and, thereby, in the reduction of the induced expression of IFN-I, TNF- α and IL-6 (Figure 5c).

2.1.2.1.7 CLEC5A

CLEC5A, also known as Myeloid DNAX activation protein 12 (DAP12)-associating lectin-1 (MDL-1), is a type II C-type lectin receptor expressed in cells of myeloid origin, like monocytes and macrophages, and in human CD66-positive neutrophils (Aoki et al., 2009). Contrarily to other CLRs predominantly involved in fungal and micobacterial recognition, CLEC5A was the first CLRs directly linked to viral recognition. It has been shown that this receptor plays a crucial role in the pathophysiology of dengue virus infection, being directly involved in the production of proinflammatory cytokines by infected macrophages (Chen et

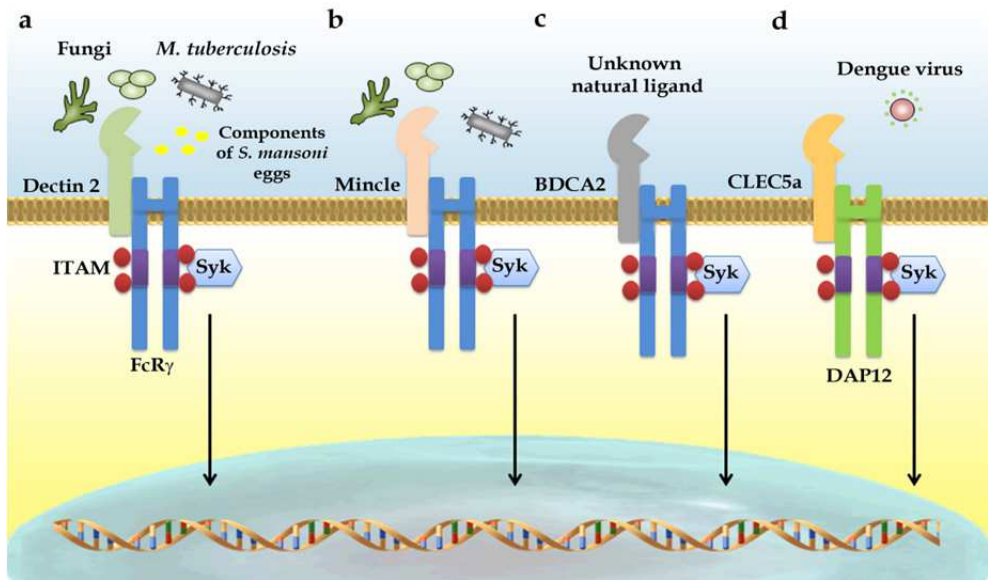


Fig. 5. Signaling through ITAM-coupled C-type lectin receptors. Dectin-2, Mincle and BDCA2 do not contain defined signaling motifs in their cytoplasmic tail being incapable of inducing intracellular signaling on their own. Following ligand binding, these receptors associate with FcR γ leading to recruitment of Syk and subsequent activation of downstream signaling cascades (black arrows). CLEC5a also lacks a cytoplasmic catalytic domain. Recognition of Dengue virions by CLEC5a, results in the association and phosphorylation of DAP12, leading to recruitment of Syk and activation of Syk-dependent downstream signaling.

al., 2008; Watson et al., 2011). CLEC5A has a very short cytoplasmic region lacking a defined signaling motif, yet it transduces intracellular signals through non-covalent association with the ITAM-bearing adapters DAP10 and DAP12 (Bakker et al., 1999; Inui et al., 2009). DAP10 ITAM motif contains a cytoplasmic sequence that facilitates PI3K recruitment and activation, being possible that it cooperates with DAP12-associated receptors to mediate costimulatory signals (Kerrigan & Brown, 2010). Moreover, it was shown that the interaction of dengue virus with CLEC5A causes the phosphorylation of the coupled DAP12 ITAM motif (Chen et al., 2008). Although not formally demonstrated, this molecular event may result in Syk recruitment and activation, followed by downstream signaling that leads to the observed induction of proinflammatory cytokines (Figure 5d)

2.1.2.1.8 DCIR

DCIR was found to be expressed at high levels in blood monocytes, myeloid and plasmacytoid DCs, macrophages and in a less extent in B cells (Bates et al., 1999). Although no endogenous or exogenous specific ligands were yet identified, the receptor was recently shown to play an important role in HIV-1 infection by acting as an attachment factor for the virus (Lambert et al., 2008). DCIR and DC-associated C-type lectin-2 (DCAL-2) are, among

the presently identified human CLRs, the only ones containing intracellular immune receptor tyrosine-based inhibition motifs (ITIMs). These ITIM motifs are responsible, in a phosphatase dependent fashion, for the negative signals that result in repressed activation of neutrophils and dendritic cells (Kanazawa et al., 2002; Richard et al., 2006).

At the molecular level, the activation of DCIR by anti-DCIR antibodies leads to receptor internalization into endosomal compartments in a clathrin-dependent process. As in these endosomal structures are also located TLR8 and TLR9, it is likely that internalized DCIR will interact with them, modulating their signaling. Supporting this hypothesis, recent data shows that the phosphorylation of ITIM promotes the recruitment of the phosphatases SH2-domain-containing protein tyrosine phosphatase 1 (SHP1) or SHP2, which, by an unidentified mechanism, leads to the downregulation of TLR8-induced IL-12 and TNF production in myeloid DCs (Meyer-Wentrup et al., 2009), and to the down-modulation of TLR9-induced IFN and TNF production in plasmacytoid DCs (Meyer-Wentrup et al., 2008).

2.1.3 RIG-I-Like receptors

RIG-I-like receptors (RLRs) constitute a family of three cytoplasmic RNA helicases: retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated gene 5 (MDA5) and laboratory of genetics and physiology 2 (LGP2). These receptors share a common functional RNA helicase domain near the C terminus (HELICc) that specifically binds to the RNA of viral origin and are, therefore, crucial for antiviral host responses (Yoneyama et al., 2004; Wilkins & Gale, 2010). These responses result from the action of induced inflammatory cytokines and type I interferons over the cells of the innate and adaptive immune system. Inflammatory cytokines primarily promote the recruitment of macrophages and dendritic cells, while type I interferons inhibit viral replication, promote the apoptosis of infected cells and increase the lytic capacity of natural killer cells (Takahasi et al., 2008).

RIG-I is involved in the recognition of a wide variety of RNA viruses belonging to the paramyxovirus and rhabdovirus families, as well as Japanese encephalitis virus, while MDA5 specifically detect, Picornaviruses, such as encephalomyocarditis virus, mengovirus and poliovirus. Some virus such as dengue virus and West Nile Virus, require, however, the activation of both RIG-I and MDA5 to generate a robust innate immune responses.

Despite structural similarity, RIG-I and MDA5 have been shown to bind distinct types of viral RNAs (Kato et al., 2006). MDA5 preferentially binds long dsRNAs, whilst RIG-I has high affinity for 5'-triphosphate ssRNAs and short dsRNAs without a 5'-triphosphate end (Pichlmair et al., 2006; Kato et al., 2008; Lu et al., 2010). The RIG-I distinction of self from viral ssRNAs is ensured by the predominantly nuclear localization of cellular 5'-triphosphate ssRNAs that even if present in the cytoplasm are normally capped or processed. Recently, the notion that 5'-triphosphate ssRNAs were sufficient to bind to and activate RIG-I was challenged by data obtained with synthetic single-stranded 5'-triphosphate oligoribonucleotides (Schlee et al., 2009). In these experiments, the synthetic 5'-triphosphate ssRNAs were unable to activate RIG-I and only the addition of the synthetic complementary strand resulted in optimal binding and activation of the receptor. The authors hypothesized that this newly data explains how RIG-I detects negative-strand RNA viruses lacking long dsRNA but containing blunt short double strand 5'-triphosphate RNA in the panhandle region of their single-stranded genome.

2.1.3.1 Signaling through RIG-I-Like receptors

RIG-I and MDA5 contain a DExD/H-box helicase domain that recognizes the viral RNA, inducing conformational changes and exposing the caspase-recruitment domains (CARDs) responsible for downstream signaling of these cytoplasmic sensors. CARDs interact with a CARD-containing adaptor, IFN- β promoter stimulator-1 (IPS-1), located in the outer mitochondrial membrane and on peroxisomes (Kawai et al., 2005; Dixit et al., 2010). While peroxisomal IPS-1 induces early expression of interferon-stimulating genes (ISGs) via transcription factor IRF1, mitochondrial IPS-1 induces delayed responses via IRF3/IRF7-controlled expression of ISGs and type I interferons. Therefore, signaling through mitochondrial and peroxisomal IPS-1 is essential to an effective antiviral response. From the interaction of IPS-1 with RIG-I and MDA5 CARDs also results the activation of NF- κ B, a process that involves the recruitment of TRADD, FADD, caspase-8, and caspase-10 and leads to the induction of proinflammatory cytokines (Takahashi et al., 2006) (Figure 6a). The third member of this cytoplasmic PRRs family, LGP2, similarly to RIG-I and MDA5, possesses a DExD/H-box helicase domain but is devoid of a CARD domain (Yoneyama et al., 2005) and was therefore considered as a negative regulator of RIG-I- and MDA5-mediated signaling (Rothenfusser et al., 2005; Komuro & Horvath, 2006; Saito et al., 2007). Recent *in vivo* experiment showed, however, precisely the opposite, suggesting that LGP2 could contribute to a robust antiviral response, acting as a facilitator of the interaction between viral RNA, RIG-I and MDA5 (Satoh et al., 2010).

2.1.4 NOD-like receptors

Nucleotide-oligomerization domain (NOD)-like receptors (NLRs) are cytosolic sensors of microbial components highly conserved through evolution. A great number of homologs of these receptors have been described in animals and plants, attesting their importance as ancestral host defense mechanisms. In humans, 23 members of the NLR family were identified, being primarily expressed in immune cells, such lymphocytes, macrophages and dendritic cells, although also found in epithelial and mesothelial cells (Franchi et al., 2009). NLRs contain three characteristic domains: a) a C-terminal leucine-rich repeat (LRR) domain, responsible for ligand sensing and autoregulation, b) a central nucleotide-binding oligomerization (NOD) domain, required for nucleotide binding and self-oligomerization upon activation and c) a N-terminal effector domain responsible for downstream signal propagation. To date, four different N-terminal domains have been identified: acidic transactivation domain, caspase-recruitment domain (CARD), pyrin domain (PYD), and baculoviral inhibitory repeat (BIR)-like domain (Chen et al., 2009). NOD1 and NOD2, the most studied NLRs, both sense bacterial molecules produced during peptidoglycan synthesis and remodeling. Peptidoglycan is a major component of the bacterial cell wall, formed by alternated residues of *N*-acetylglucosamine (GlcNAc) and *N*-acetylmuramic acid (MurNAc), which are crosslinked by short peptide chains. The bridging aminoacids inside these peptide chains are differentially found in gram-negative and gram-positive bacteria, being responsible for the differential recognition abilities of NOD1 and NOD2 (McDonald et al., 2005). Therefore, NOD2 senses muramyl dipeptide (MDP), which is found in the peptidoglycan of nearly all gram-positive and gram-negative bacteria, while NOD1 sense γ -D-glutamyl-meso-diaminopimelic acid (iE-DAP), an amino acid that is predominantly found in gram-negative bacteria and in some gram-positive bacteria, such as *Listeria monocytogenes* and *Bacillus* spp (Chamaillard et al., 2003).

2.1.4.1 Signaling through NOD-like receptors

The intracellular NLR proteins organize signaling platforms, such as NOD signalosomes and inflammasomes that trigger NF- κ B and MAPKs pathways and control the activation of inflammatory caspases (Chen et al., 2009). Upon recognition of their respective ligands, both NOD1 and NOD2 self-oligomerize to recruit and activate the serine-threonine kinase RICK that becomes polyubiquitinated. RICK directly interacts with the regulatory subunit of IKK, the inhibitor of NF- κ B kinase γ (IKK γ), promoting the activation of the catalytic subunits IKK α and IKK β (Inohara et al., 2000). These activated subunits phosphorylate the inhibitor I κ B- α , leading to its ubiquitination and subsequent degradation via the proteasome. The released NF- κ B translocates to the nucleus, where it promotes the expression of proinflammatory cytokines and chemokines (Masumoto et al., 2006; Werts et al., 2007; Buchholz & Stephens, 2008). Additionally, RICK also promotes the K63-linked polyubiquitination of IKK γ , which facilitates the recruitment of transforming growth factor β -activated kinase (TAK1) (Hasegawa et al., 2008). TAK1 forms a complex with the ubiquitin binding proteins TAK1-binding protein 1 (Tab1), Tab2, and/or Tab3, promoting the phosphorylation of the IKK β subunit of IKK, that in turn leads to the phosphorylation and degradation of I κ B- α . Signaling through NOD1 and NOD2 also results in MAPK activation by a process not fully characterized, but dependent of TAK1 and RICK (Shim et al., 2005) (Figure 6b).

Another process by which NLRs participate in host response to microbial infections is through their involvement in inflammasome formation. Inflammasomes are large protein complexes that includes NLRs proteins, the adapter ASC (apoptosis-associated speck-like protein containing a C-terminal CARD) and pro-caspase-1. This molecular platform is crucial for caspase-1 activation and subsequent processing of pro-IL-1 β and pro-IL-18, resulting in the secretion of their mature biologically active forms (Lamkanfi et al., 2007). NLR family members, such as NLRP1, NLRP3 and NLRP4, have shown to be critical factors in the activation of proinflammatory caspase-1 and IL-1 β secretion in response to several microbial stimuli (Pedra et al., 2009) (Figure 6b).

NLR signaling: NOD1 senses iE-DAP, an amino acid predominantly found in gram-negative bacteria while NOD2 senses MDP, which is found in the peptidoglycan of nearly all gram-positive and gram negative bacteria. Following recognition of their respective ligands, both NOD1 and NOD2 self oligomerize to recruit and activate RICK, which in turn activates NF- κ B via the IKK complex. Signaling through NOD1 and NOD2 also results in MAPK activation by a process not fully characterized but dependent of TAK1 and RICK. Another member of the NLR family constitutes the inflammasome, a multi-protein complex that includes NLRs proteins, the adapter ASC and pro-caspase-1(pC1). In this complex pro-caspase 1 is activated, promoting in turn the maturation of pro-IL-1 β cytokine to its bioactive form.

3. Molecular mechanisms by which microorganisms subvert the innate immune system

Common features of pathogenic microorganisms are the exploitation of cytoskeleton and membranous structures to invade/or to gain motility inside the host cell, and also the manipulation of key signaling pathways. In this section, we will specially focus on the mechanisms by which pathogens manipulate signaling pathways in immune cells.

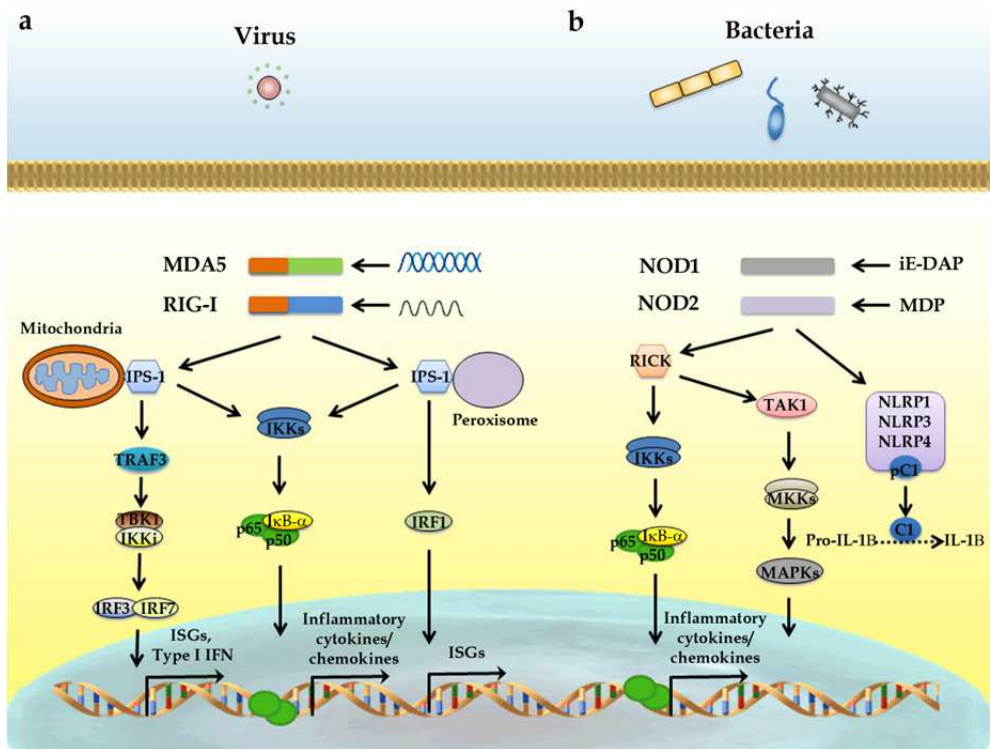


Fig. 6. Signaling through RLRs and NLRs. RLR signaling: RIG-I and MDA5 function as cytosolic sensors of viral RNA, recognizing preferentially 5'-triphosphate ssRNAs and long dsRNAs, respectively. Binding of viral RNAs to these receptors activates signaling through the adaptor protein IPS-1, located in the outer mitochondrial membrane or on in peroxisomes. Mitochondrial IPS-1 leads to activation of NF-κB and IRF3/IRF7 through the IKK complex and TBK1/IKKi, respectively, which results in the production of inflammatory cytokines, type I interferons and interferon-stimulating genes (ISGs). In turn, peroxisomal IPS-1 induces early expression of ISGs via transcription factor IRF1.

As stated in above sections, pattern-recognition receptors confer to mammals an extremely efficient “detection system” of invading microorganism, triggering an intricate signaling network that ultimately orchestrates the establishment of an adequate immune response. However, as part of their pathogenic strategies, several microorganisms evade immune system by circumventing, or distorting, these signaling pathways and creating, therefore, conditions that facilitate their replication and spreading in the host. In the last few years great efforts have been made to understand the molecular mechanisms behind this subversion, and various signaling cascades were identified as main targets of pathogens and virulence factors. When globally analyzed, cascade signals downstream PPRs activation mainly converge to two key signaling pathways: the transcription factor nuclear factor-κB (NF-κB) and the mitogen activated protein kinases (MAPKs). NF-κB is a cornerstone of innate immunity and inflammatory responses, controlling the expression of effector

molecules, such as proinflammatory cytokines/chemokines, anti-apoptotic factors and defensins; MAPKs are also signaling cascades intimately connected to the regulation of innumerable aspects of immunity. Therefore it is expected that pathogens try to circumvent, or manipulate, these pathways. This manipulation can be achieved by directly targeting signaling intermediates (through cleavage or dephosphorylation), or by distorting the balance between immunogenic and tolerogenic signals. The latter mechanism mostly results from the exploitation of signaling crosstalk between several receptors of the innate immune system (Hajishengallis & Lambris, 2011). A classical example is the crosstalk between TLRs and DC-SIGN: while antigen recognition by TLRs triggers a deleterious response, recognition of another antigen of the same pathogen by DC-SIGN negatively modulates the TLR signal, promoting an unresponsive state. In the present chapter we do not intend to cover the general immune evasion strategies of pathogens, but rather focus on the mechanisms by which the microorganisms directly, or by “crosstalk manipulation”, interfere with key immune signaling pathways.

3.1 Exploiting CLRs signaling and their crosstalk with other receptors

Mycobacterium tuberculosis, the causative agent of tuberculosis, has been a major world-wide threat for centuries. In 2009 the disease was responsible for 1.8 million deaths and a recent estimate suggests that a third of the world's population is infected (WHO 2010). Macrophages are the primary targets for *M. tuberculosis* and mainly drive the initial innate immune response against the pathogen, while dendritic cells play a central role in the establishment of a subsequent cellular response (Fenton & Vermeulen, 1996; Demangel & Britton, 2000). In this process, DCs capture and process the pathogen, migrate to draining lymph nodes and present the antigenic peptides to naïve T cells, initiating an adaptive immune response. *M. tuberculosis* was shown to modulate the functions of both macrophages and DCs (Balboa et al., 2010; Geijtenbeek et al., 2003), promoting immune conditions that allow a latent infection. Macrophages phagocytose bacteria into phagosomes, which then mature by acquiring low pH, degradative enzymes and reactive oxygen/nitrogen species. Phagosomes fuse with lysosomes to form phagolysosomes, exposing the engulfed microorganism to the lethal action of hydrolases, proteases, superoxide dismutase and lysozymes. However, *M. tuberculosis* escapes death by blocking the maturation of phagosomes and preventing their fusion with lysosomes (Fratti et al., 2003; Hmama et al., 2004). This process was shown to be partially mediated by the binding of mannosylated lipoarabinomannan (ManLAM) to the mannose receptor in macrophages (Kang et al., 2005). ManLAM is a major mannose-containing lipoglycan present in *M. tuberculosis* cell wall that downregulates calmodulin-dependent signal transduction and inhibits sphingosine kinase, preventing the conversion of macrophage sphingosine to sphingosine-1 phosphate (S-1P) (Malik et al., 2003). This arrests the S-1P-dependent increase in Ca^{2+} concentration, disrupting the PI-3K signaling and the subsequent recruitment of Rab5 effector early endosomal antigen 1 (EEA1) to phagosomes (Fratti et al., 2001). EEA1 is crucial for the delivery of lysosomal components from the trans-Golgi network to the phagosome and regulates fusion of phagosomes with lysosomal vesicles. Therefore the MR-mediated phagocytosis of ManLAM-containing *M. tuberculosis* prevents phagosomes from maturing and fusing with lysosomes, allowing bacteria to survive.

One of the most ingenious mechanisms used by microorganisms to escape host immune response is to subvert or disrupt the molecular signaling crosstalk between receptors of the innate immune system (Hajishengallis & Lambris, 2011).

This signaling hijacking frequently leads to an augmented production of immunosuppressive molecules, such as IL-10 and/or to a decreased expression of proinflammatory molecules, such IL-12 and IFN.

Both *M. tuberculosis* and *M. bovis* BCG are able to induce DC maturation through TLR2- and TLR4-mediated signaling (Henderson et al., 1997; Tsuji et al., 2000). However, the concomitant engagement of ManLAM to the C-type lectin receptor DC-SIGN modulates the TLR-induced NF- κ B activation, blocking the expression of co-stimulatory molecules CD80, CD83 and CD86 and inducing the production of the immunosuppressive cytokine IL-10 (Geijtenbeek et al., 2003; Gringhuis et al., 2007). Immature mycobacteria-infected DCs and IL-10 dependent blockage of IL-12 production impair the generation of a protective Th1 response, contributing therefore to the establishment of a latent infection. Besides *M. tuberculosis*, other important human pathogens, such *M. leprae*, *Candida albicans*, measles virus and HIV-1, were shown to explore TLR-DC-SIGN crosstalk to induce the expression of the immunosuppressive cytokine IL-10 (Bergman et al., 2004; Gringhuis et al., 2007; Gringhuis et al., 2009). Similarly to *M. tuberculosis*, HIV-1 activates the Raf-1 pathway through DC-SIGN, modulating TLR signaling, and leading to IL-10 increased production, impairment of TLR-induced dendritic cell maturation and reduced T-cell proliferation. In a process independent of TLR activation, DC-SIGN interacts with HIV-1 envelope glycoprotein gp120, and regulates the gene expression profile of DCs (Hodges et al., 2007). Among the modulated genes, activating transcription factor 3 (ATF3) is of particular importance since it acts as a negative regulator of TLR4-induced expression of proinflammatory cytokines IL-6 and IL-12 (Gilchrist et al., 2006). This is therefore suggestive that DC-SIGN, besides modulating, also represses TLR4 signaling (den Dunnen et al., 2009). Additionally, HIV-1 also exploits the crosstalk between DCIR and TLR8/TLR9 to promote DC infection and to evade host immune response. Binding of the virus to DCIR was shown to down-modulate the production of TLR8-induced IL-12 and TLR9-induced IFN- α , in myeloid and in plasmacytoid DCs, respectively.

In contrast to the above referred mannose-containing pathogens (mycobacteria, *C. albicans* and HIV-1), *Helicobacter pylori* induces IL-10 production and Th1 inhibition, through a Raf-1 independent mechanism. In fact, binding of the fucose-containing LPS Lewis antigens from *Helicobacter pylori* to DC-SIGN actively dissociated the KSR1–CNK–Raf-1 complex from the DC-SIGN signalosome, modifying downstream signal transduction (Gringhuis et al., 2009). Recently, a new form of crosstalk between DC-SIGN and TLRs was described in dendritic cells (Hovius et al., 2008). In this process, *Borrelia burgdorferi* lipoproteins trigger TLR2 activation, while Salp15, a salivary protein from *Ixodes scapularis*, the human vector of *B. burgdorferi*, binds to DC-SIGN and leads to RAF1-mediated MEK activation. MEK-dependent signaling attenuates, in turn, the TLR2-induced proinflammatory cytokine production, by enhancing the decay of *Il6* and *Tnf* mRNA and decreasing IL-12p70 cytokine production. Additionally, this crosstalk synergistically enhances IL-10 production. This immunosuppression reveals to be advantageous for both, the vector and the bacteria, given that it impairs the establishment of an effective adaptive immune response against tick and/or *B. burgdorferi* antigens (Hovius et al., 2008).

In neutrophils, mycobacteria bind, to a yet unidentified C-type lectin receptor (potentially CLEC5A) and induce, via Syk, a crosstalk with the TLR2 adapter molecule MYD88. This results in a rapid and synergistic phosphorylation of Akt and p38 MAK, leading to increased IL-10 production, that in turn contributes to the persistence of high mycobacterial burden (Zhang et al., 2009). Finally, another example of CLR-TLRs crosstalk that could contribute to the successes of invading pathogens was recently characterized (Goodridge et al., 2007). The C-type lectin receptor Dectin-1 is, in DCs and macrophages, crucial for the detection of the pathogenic fungi *Candida albicans*, *Aspergillus fumigates* and *Pneumocystis carinii*. Traditionally, regarded as inflammatory stimuli, ligands of Dectin-1 induce significant amounts of the anti-inflammatory cytokine IL-10, conditioning inflammatory cytokine production and Th subsets polarization. The receptor collaborates with TLR2 in NF- κ B activation, inducing proinflammatory cytokines, such as IL-6 and TNF- α (Gantner et al., 2003). However, engagement of Dectin 1 was also shown to activate the nuclear factor of activated T-cells (NFAT) that, directly and/or by interference with TLR2, regulates the expression of the immunosuppressive cytokine IL-10 (Goodridge et al., 2007). Moreover, Dectin-1, due to its cytoplasmic adapter ITAM, signals in an autonomous manner, leading to IL-10 production through a calcium-dependent calmodulin (CaM) dependent kinase (CaMK)-Pyk2-ERK signaling pathway (Kelly et al., 2010). Accordingly, the genetic deletion of Dectin-1 only partially blocks inflammatory cytokine production, while severely impairs IL-10 expression (Taylor et al., 2007).

3.2 Exploiting TLRs signaling and their crosstalk with other receptors

Among pattern recognition receptors, TLRs are, by excellence, the orchestrators of innate immunity. However, pathogens might have evolved to interact with, and exploit, TLRs signaling cascades, inducing conflicting signals by distinct pathogen-expressed TLR ligands. TLR2-induced responses represent a paradigm of this TLR-TLR interplay. Signaling through this receptor leads to an overall proinflammatory response, however it also induces the production of substantial levels of the immunosuppressive cytokine IL-10. It was hypothesized that this probably results from the crosstalk between TLR2 and particular co-receptors such CLRs (Zhang et al., 2009).

Several microorganisms exploit TLR2 crosstalk with other TLRs to evade immune system. For example, in macrophages, *C. albicans* was shown to trigger both TLR4 and TLR2 signals. While TLR4 signaling confers protection against infection, TLR2 signaling promotes host susceptibility to invasive candidiasis, through the induction of high levels of IL-10 (Netea et al., 2004). Lipoproteins from *M. tuberculosis* cell wall bind TLR2 and down-regulate the bacterial CpG DnA-TLR9 induced production of IFN α and IFN β (Simmons et al., 2010). Similarly, in human monocytes, Hepatitis C virus induces TLR2-mediated expression of IL-10, which in turn suppresses TLR9-induced IFN α production by plasmacytoid DCs (Dolganic et al., 2006). The pathogens *M. tuberculosis* and *Toxoplasma gondii* promote their survival in macrophages, through TLR2-MYD88-dependent induction of IL-6, IL-10 and granulocyte colony-stimulating factor (GCSF) (El Kasmi et al., 2008). These cytokines, through signal transducer and activator of transcription 3 (STAT3), increase the expression of arginase 1 (ARG1), which by competing with inducible Nitric Oxide Synthase (iNOS) for the common substrate arginine, inhibits the TLR4-mediated production of nitric oxide (NO) (Qualls et al., 2010).

Additionally to interfering with PPR signaling crosstalk, microorganisms also exploit the interplay between other immune receptors, such as TLRs and complement receptors. Normally, complement receptors and TLRs are rapidly activated in response to infection, and their signals synergistically converge to activate ERK and JNK, promoting an effective early innate immune response. However, in macrophages this crosstalk between TLRs and complement receptors is frequently subversive, particularly by reducing the cytokines of IL-12 family (IL-12, IL-23, and IL-27). This decreased cytokine expression translates into a limited polarization of protective Th1 responses (Hawlich et al., 2005). The molecular mechanisms of this crosstalk are not fully known, but anaphylatoxin receptor C5aR was shown to interfere with TLR-induced cytokine expression, by ERK and PI3K-dependent pathways. The C5aR-ERK-IRF1 pathway preferentially inhibits IL-12p70 production, while the C5aR-PI3k-IRF8 pathway mainly decreases the production of IL-23 (Hawlich et al., 2005). Several other complement receptors, such as gC1qR, CD46 and CR3, limit the TLR4 and TLR2-induced IL-12 production (Karp et al., 1996; Marth & Kelsall, 1997). HCV core protein has been shown to associate with the putative gC1q receptor expressed in host immune cells, specifically inhibiting TLR-induced production of IL-12. Therefore, engagement of gC1qR on DCs by HCV depresses Th1 immunity and contributes to viral persistence (Waggoner et al., 2007). *L. monocytogenes* and *S. aureus* were also shown to interact with gC1qR, leading probably to a similar evasion mechanism (Braun et al., 2000; Nguyen et al., 2000). Other human pathogens, such as *P. gingivalis*, *Histoplasma capsulatum* and *B. pertussis* inhibit IL-12 release through CR3-TLR-dependent crosstalk. The fimbriae of *Porphyromonas gingivalis* interacts with complement receptor 3, activating ERK1 and ERK2, and thereby limiting TLR2-induced IL-12 production (Hajishengallis et al., 2007).

These are only some examples of molecular mechanisms by which microorganisms disrupt, or subvert, signaling crosstalk between innate immune receptors, being particularly emphasized in this review the PPRs interplay. This is an exciting and dynamic Immunology field that in last decade brought considerable advances to the understanding of the pathophysiology of several human infectious diseases.

3.3 Direct targeting of signaling intermediates

Another common evasive maneuver used by pathogens is to directly impair signal transduction, through cleavage or dephosphorylation of intermediate molecules in signaling cascades. Cascade signals downstream PPRs activation mainly converge to NF- κ B and MAPKs pathways to establish effective immune responses, making the intermediates of these pathways main targets of microorganism hijacking strategies.

Phosphorylation is the most frequent intracellular modification for signal transduction and many pathogens modulate host cell phosphorylation machinery, in order to block or circumvent deleterious signals. *Yersinia* species, causative agents of human diseases, such as bubonic and pneumonic plagues and gastrointestinal disorders, use a wide spectrum of strategies to circumvent immune response. Through a type III secretion system, bacteria can inject into the cytosol of the host cell six different *Yersinia* outer proteins (Yop). These effector proteins interfere with signaling pathways involved in the regulation of the actin cytoskeleton, phagocytosis, apoptosis and the inflammatory response, thus favoring survival of the bacteria (Viboud & Bliska, 2005). The protein YopP/J was shown to be the main antiinflammatory effector protein of *Yersinia*, by inactivating MAPKs and NF- κ B

pathways. NF- κ B pathway inhibition was initially clearly associated to the de-ubiquitinating activity of YopP/J. I κ B- α de-ubiquitination impairs its targeting for proteosomal degradation, effectively sequestering NF- κ B into the cytoplasm (Zhou et al., 2005). However, this ubiquitin-like protease activity was unable to explain the effects of YopP/J over MAPKs, as ubiquitination is not known to play a direct role in MAPK signaling. Recent data demonstrate that YopP/J has acetyltransferase activity, transferring acetyl moieties to Ser/Thr residues in the activation loop of MKKs and IKKs (Mittal et al., 2006). It was suggested that acetylation competes effectively with phosphorylation at these sites, thereby blocking signal transduction. *Vibrio* outer protein A (VopA), an YopJ-like protein from *Vibrio parahaemolyticus*, was also shown to selectively inhibit MAPKs signaling by acetylating a conserved lysine in the ATP-binding pocket of MKKs. This not only prevents MKKs activation but also decreases the activity of activated MKKs (Trosky et al., 2007).

Salmonella, another important human pathogen, delivers effector proteins into host cell, suppressing cellular immune response through blockade of NF- κ B and MAPKs cascades (McGhie et al., 2009). The effector protein SptP, by its GTPase-activating protein and tyrosine phosphatase activities, reverses MAPKs activation (Murli et al., 2001; Lin et al., 2003) and AvrA, through its acetyltransferase activity toward specific mitogen-activated protein kinase kinases (MAPKKs), potently inhibits JNK (Jones et al., 2008). Other *Salmonella* effector proteins, such SpvC, a phosphothreonine lyase, directly dephosphorylates ERK, JNK and p38 MAPKs (Mazurkiewicz et al., 2008) and Avra and SseL proteins suppress NF- κ B activation by impairing I κ B- α ubiquitination and degradation (Ye et al., 2007; Le Negrate et al., 2008).

Similarly, as a strategy for repressing innate immunity, *Shigella flexneri* has evolved the capacity to precisely modulate host cell epigenetic "information", interfering with MAPKs and NF- κ B pathways at several points. This is mainly driven by the effector protein OspF. OspF is remarkable not only for its biochemistry but also for the fact that is one of the few bacterial effectors that is known to translocate to the host-cell nucleus. At the cytosol level, the protein binds to the ubiquitylated form of the E2 ubiquitin-conjugating enzyme UBCH5B, and independently of I κ B phosphorylation, prevents the transfer of ubiquitin to I κ B by an E3 ubiquitin-protein ligase (Kim et al., 2005). Additionally, OspF dephosphorylates ERK and p38 MAPKs by either phosphatase (Arbibe et al., 2007) or phosphothreonine lyase (Li et al., 2007) activities. Recent data showed that this protein also manipulates the physical and spatial context of DNA encoding NF- κ B-responsive genes (Arbibe et al., 2007). At the host-cell nucleus, OspF dephosphorylates the MAPK ERK2, impairing the activation of mitogen- and stress-activated kinase 1 (MSK1) and MSK2. This prevents subsequent histone phosphorylation, which is necessary for NF- κ B-dependent transcription. Therefore, several innate immune-related genes under control of NF- κ B remain silent, allowing *S. flexneri* to avoid a deleterious response.

The mechanisms used by microorganisms to modulate NF- κ B signaling are diverse and, as exemplified above, a common strategy is to target the steps that lead to I κ B degradation. However, several pathogens, such *Toxoplasma gondii* and *Leishmania spp* have evolved distinct processes to block this central signaling pathway. Infection by *T. gondii* provides potent signals for IL-12 production and for induction of strong Th1 immunity, being NF- κ B an important player in this process (Caamano & Hunter, 2002). However, at early times of infection (up to 24h) the parasite impairs in macrophages, the NF- κ B signaling, limiting the production of IL-12, TNF- α and NO. This blockage was shown to occur independently of

infection-induced IKK-dependent degradation of I κ B- α , resulting in specific impairment of NF- κ B nuclear translocation. The termination of NF- κ B signaling was therefore associated with reduced phosphorylation of p65/RelA subunit, an event involved in the ability of NF- κ B to translocate to the nucleus and to bind DNA (Shapira et al., 2005).

Regarding *Leishmania*, the infection by this protozoan parasite has long been regarded as the paradigm of a Th2 immune response. Extensive studies have been conducted to disclose the molecular mechanism by which *Leishmania* modulate intracellular signaling events in infected macrophages and dendritic cells. Obtained data indicate that the parasite use an extensive "arsenal" of strategies and virulence factors to alter the host cell signaling, favoring its survival. Infection of macrophages with *L. donovani* promastigotes was shown to increase intracellular ceramide content causing a downregulation of classical PKC activity, up-regulation of calcium independent atypical PKC-zeta and dephosphorylation of ERK. Downregulation of ERK signaling was subsequently found to be associated with the inhibition of activated protein 1 (AP-1) and NF- κ B transactivation (Ghosh et al., 2002). Other studies with the same infection model showed that *Leishmania* alters signal transduction upstream of c-Fos and c-Jun, by inhibiting ERK, JNK and p38 MAP Kinases, resulting in a reduction of AP-1 nuclear translocation (Prive & Descoteaux, 2000). Until recently, little was known about the intervenients and molecular mechanisms behind these immunosuppressive abilities of *Leishmania*. In macrophages infected with *Leishmania mexicana* amastigotes, Cameron and co-workers showed that cysteine peptidase B (CPB) is the virulence factor responsible for proteolytic degradation of NF- κ B, ERK and JNK (Cameron et al., 2004). Additionally, CPB is also involved in the activation of host protein tyrosine phosphatase 1B (PTP-1B), inhibition of AP-1 and cleavage of STAT-1 α (Abu-Dayyeh et al., 2010). Another *Leishmania* virulence factor, the surface metalloprotease GP63, was shown to cleave host protein tyrosine phosphatases PTP-1B, TCPTP, and SHP-1, resulting in the stimulation of their phosphatase activity and consequent dephosphorylation of key kinases, such as JAK/STAT, IRAK-1 and MAPKs (Gomez et al., 2009). Moreover, GP63 is also responsible for the observed cleavage of NF- κ B p65^{RelA} subunit in *L. mexicana* and *L. infantum* -infected macrophages and dendritic cells (Gregory et al., 2008; Neves et al., 2010). From this cleavage results a fragment of approximately 35 kDa that is rapidly translocated into the nucleus where it has some transcriptional activity. It was postulated that the resulting p35^{RelA} fragment may represent an important mediator by which *Leishmania* promastigotes induce several chemokines without inducing other NF- κ B-regulated genes, such as iNOS and IL-12 that are detrimental for parasite survival.

Recently, the metalloprotease GP63 was shown to be involved in the decreased general translation observed in macrophages infected with *L. major* (Jaramillo et al., 2011). The parasite protease cleaves the serine/threonine kinase mammalian/mechanistic target of rapamycin (mTOR), impairing the formation of mTOR complex 1 (mTORC1) and the downstream phosphorylation of translational repressor 4E-binding protein 1/2 (4E-BP1/2). The activity of the translational repressors 4E-BPs is controlled through their phosphorylation state and, in normal conditions, mTORC1 formation leads to hyperphosphorylation of 4E-binding proteins (4E-BPs), causing their dissociation from eukaryotic initiation factor 4F, facilitating this way the translation of mRNA (Gingras et al., 1999). mTORC1, through its downstream targets p70 ribosomal S6 protein kinases 1 and 2 (S6K1/2) and 4E-BPs controls the translation of key innate immune effector molecules, such as type I IFN (Cao et al., 2008; Costa-Mattioli &

Sonenberg, 2008). This cleavage of mTOR by Leishmania GP63 represents, therefore, a survival mechanism where the parasite directly targets the host translational machinery. This strategy is also a common feature of several human viruses. Lytic viruses, such members of the picornavirus group (enterovirus, rhinovirus and aphtovirus) inhibit overall host cellular translation, redirecting the translational apparatus to viral protein synthesis. This effect was shown to be due to the poliovirus 2A protease-mediated cleavage of the translation initiation factor eIF4G (Borman et al., 1997).

Bacillus anthracis, *Chlamydia* and *Escherichia coli* are examples of other human pathogens that directly cleave intermediate molecules from NF- κ B and MAPKs signaling cascades. *Bacillus anthracis*, a spore-forming encapsulated gram-positive bacterium known to cause anthrax disease, produces innumerable virulence factors critical for the establishment of infection and pathogenesis (Turnbull, 2002). Among these factors, the plasmid-encoded enzymes lethal factor (LF) and oedema factor (OF) are of major importance for the evasion abilities of *B. anthracis*. LF is a particularly selective metalloproteinase that cleaves MKKs at specific sites outside of their catalytic domains, impairing the downstream MAPK activation (Duesbery et al., 1998). In addition, it blocks the p38 MAPK-dependent activation of IRF3 (Dang et al., 2004) and, although not directly affecting NF- κ B activity, it causes the downregulation of NF- κ B target genes that simultaneously require p38 activity for induction (Park et al., 2002). Consequently, macrophage production of proinflammatory cytokines, such as TNF- α , IL-1 β and IL-6, is severely impaired. In turn, OF is an active Ca²⁺ and calmodulin-dependent adenylate cyclase that increases cAMP in the cytosol of host cells (Drum et al., 2002). Raised intracellular levels of cAMP activate PKA, causing downstream inhibition of ERK and JNK pathways, as well as a decreased NADPH oxidase activity, resulting in impaired TNF- α and microbicidal superoxide production (Hoover et al., 1994).

The obligate intracellular bacterial parasite *Chlamydia* is the leading cause of preventable blindness worldwide and urogenital tract infection remains the most prevalent cause of sexually transmitted diseases in developed countries. The parasite avoids host inflammatory response, partially by disrupting the NF- κ B signal resultant from the PPR recognition of bacterial component such as LPS. This blockage was shown to result from the selective cleavage of the p65^{RelA} subunit of NF- κ B by the chlamydial protease-like activity factor (CPAF) (Christian et al., 2010). Similarly, *E. coli* decreases production of proinflammatory cytokines and reduces macrophage bactericidal activity, by targeting NF- κ B signal transduction at multiple points. Infection by *E. coli* induces a host caspase 3-mediated cleavage of p65^{RelA}, by a mechanism not completely defined, but thought to be mediated through the mitochondrial pathway of apoptosis (Albee & Perlman, 2006). In addition, several studies have recently demonstrated that *E. coli* also downregulates NF- κ B-mediated gene expression by injecting into host-cells several non-LEE encoded (Nle) effector proteins, such as NleB, NleC and NleE. NleB and NleE prevent IKK β activation and consequently the degradation of I κ B- α , thus limiting p65 translocation to the nucleus (Nadler et al., 2010; Newton et al., 2010) while the zinc-dependent metalloprotease NleC was shown to enzymatically degrade p65^{RelA} and JNK (Yen et al., ; Baruch et al., 2010).

Although more frequent in bacteria, the shutdown of PPR signaling by direct cleavage of cascade intermediates is also a strategy used by some relevant human viral pathogens. As an example, hepatitis C virus-host interactions have revealed several evasion mechanisms

used by the virus to control PPRs signaling, providing a molecular basis for viral persistence. In viral infections, recognition of pathogen associated molecular patterns by TLRs and RLRs leads, through independent signaling cascades, to the activation of transcription factors, such as IRF1, IRF3, IRF5, IRF7 and NF- κ B. The activity of these transcription factors is crucial for an effective antiviral innate immune response, given that they control the expression of interferon-stimulated genes (ISGs) and type I interferons. Hepatitis C virus (HCV) has evolved to disrupt RLRs signaling by impairing RIG-I pathway, through NS3/4A-mediated cleavage of IPS-1 (Malmgaard, 2004). NS3/4A is formed by a complex of the NS3 and NS4A HCV proteins and has been shown to be an essential viral protein with serine protease activity (Brass et al., 2008). In HCV infection, cleavage of IPS-1 by NS3/4A impairs downstream activation of IRF-3 and NF- κ B, blocking the production of IFN- β , as well as the expression of ISGs (Li et al., 2005). This results in a strongly compromised innate immune response, potentiating the propagation of chronic HCV infection.

4. Conclusions

Millenary host-microbe co-evolution has resulted in the development of ingenious strategies by pathogens in order to successfully evade host immune response. Besides the manipulation of host-cell cytoskeleton to gain entry and/or to gain motility in the cell, immune-cell signaling pathways are frequent targets of invading pathogens. Within the past decades, remarkable progress has been made in our understanding on how immune cells sense microorganisms and how microbial effectors counteract innate immune responses. Recognition of conserved microorganism patterns by PRRs activates, in immune cells, an intricate signaling network that culminates in the expression of effector molecules, such as cytokines, chemokines and reactive oxygen species, crucial elements to mount an adequate immune response. A common strategy of pathogens is to disrupt these signaling cascades, by promoting contradictory signals through engagement of distinct PRRs and/or by directly target intermediate components of these signaling pathways. Therefore, understanding the molecular mechanisms used by pathogens to exploit the host signaling networks is of crucial importance for the development of rational interventions in which host response will be redirect to achieve protective immunity.

5. References

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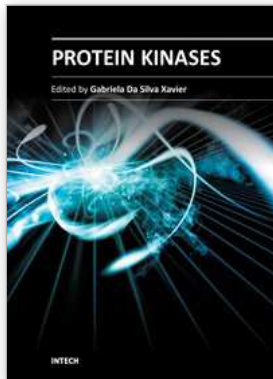
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Proteins are the work horses of the cell. As regulators of protein function, protein kinases are involved in the control of cellular functions via intricate signalling pathways, allowing for fine tuning of physiological functions. This book is a collaborative effort, with contribution from experts in their respective fields, reflecting the spirit of collaboration - across disciplines and borders - that exists in modern science. Here, we review the existing literature and, on occasions, provide novel data on the function of protein kinases in various systems. We also discuss the implications of these findings in the context of disease, treatment, and drug development.

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