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Review

Dendritic cell functions: Learning from microbial evasion strategies

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ABSTRACT

Dendritic cells (DCs) are specialized antigen presenting cells (APC) that are fundamental to initiate both immunity and tolerance. DCs play a 'sentinel' role to protect our body from potential pathogens and induce tolerogenic responses toward harmless antigens. The flexibility of DCs or macrophages to adapt to the environment and to respond accordingly can be hijacked by pathogens for their own interest to transform a potentially immunogenic APC into a tolerogenic cell with clear consequences in pathogen clearance. While these immune evasion mechanisms can be detrimental for the host, they can highlight important molecular pathways in DCs necessary for their function. In this review we will mention several mechanisms employed by pathogens to evade DC patrolling function.

1. Introduction

Dendritic cells (DCs) are specialized antigen presenting cells (APC) that are fundamental to initiate both immunity and tolerance [1]. DCs are located at the interfaces between our body and the external world [2]. Here they play a 'sentinel' role to protect our body from putative aggressors [3,4], but they can also induce tolerogenic responses toward harmless antigens [5]. Interestingly, the different function of DCs is dictated by several factors, including the 'polarization' obtained in the tissue of origin [6], their maturation state [7], the subset of analyzed DCs and macrophages [8] and the encounter with different external cues [9].

The characteristic of DCs or macrophages to quickly adapt to changes in the microenvironment renders them particularly susceptible to pathogens that can interfere with APC flexibility and transform the functionality of these cells to their own interest [10].

While these immune evasion mechanisms can be detrimental for the host, they can highlight important molecular pathways in dendritic cells necessary for their function. In this review, we will discuss several mechanisms employed by pathogens to evade DC patrolling function. These evasion mechanisms can affect antigen uptake, survival within phagolysosomes, antigen processing and presentation, DC maturation and cytokine production. This review is intended to give an overview on the different strategies adopted by pathogens rather than being an exhaustive analysis on all the different microbes capable of evading the immune surveillance by antigen presenting cells.

2. The family of APCs

APCs are fundamental to orchestrate the immune response to pathogens and to establish tolerance to harmless antigens. These complex tasks are accomplished by a whole family of APCs, whose function differ according to the tissue of origin [4]. APC subsets derive from bone marrow progenitors that seed peripheral organs or secondary lymphoid tissues where they receive instructions that make these cells 'specialized' for that particular organ or tissue [3,4]. Hence, APC subsets with shared common markers may have opposite functions if isolated from different tissues or organs. Hence, when analyzing a particular activity or immune evasion strategy adopted by microorganisms in order to avoid immunity, one has always to consider the type of APCs that is targeted.

Most of the studies that are found in the literature are based on in vitro interactions between pathogens and APCs, particularly DCs, derived from bone marrow precursors. These studies have an important relevance on the general functions of APCs, such as antigen uptake, processing and presentation, cell maturation, T-cell activation, but not always reflect the possible outcome that might occur when APCs are properly located in a tissue context. Indeed, the response to microorganisms by blood or gut APCs may be completely different as intestinal APCs are exposed to continuous environmental changes linked to the diet and to a load of resident microorganisms. Gut APCs are a classical example of cells specialized to cover the functions required in such a complex

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environment. There are at least four different subsets characterized by the expression of the integrin CD11c [11–13]. These include classical DCs, inflammatory DCs and CD11c$^+$ macrophages. CD11c$^+$ cells can differ both in function and in their ontogeny as they can differentiate from either DC precursors or monocytes. A population of classical DCs differentiates from blood pre-DCs [14] [15] and is characterized by the expression of the αE integrin CD103. Within this populations two additional subsets can be distinguished based on the expression of CD11b [14]. Lamina propria CD11b$^+$CD103$^+$ are tolerogenic cells as they can drive the differentiation of T regulatory (Treg) cells.

Under steady-state, monocytes reach the gut from the blood circulation and give rise to CD11c$^+$CX3CR1^{high}F4/80$^+$ macrophages that have tolerogenic properties [16]. These peculiar macrophages express interleukin-10 (IL-10) that allows restimulation of Treg in the lamina propria [17] and inhibits T cell expansion via a contact dependent mechanism [18]. CD11c$^+$ macrophages do not migrate out of the gut [19], a characteristic conferred by the microbiota [20]. Indeed, in mice treated with antibiotics to eliminate most of the microbiota CD11c$^+$ macrophages can migrate to the mesenteric lymph nodes, suggesting that the microbiota, via mechanisms that are still unknown, trap macrophages into the gut [20]. By contrast, during inflammation monocytes differentiate into inflammatory DCs (CD11c$^+$CX3CR1^{int}) [16,21]. Inflammatory DCs produce large quantities of mediators of inflammation (including IL-12, IL-23, inducible nitric oxide synthase (iNOS) and tumor necrosis factor (TNF)), and differently from macrophages migrate to the draining lymph node to activate T helper-1 (Th1) T cells [16].

Hence, APCs in the gut cooperate in order to induce tolerance and immunity as macrophages are specialized in antigen capture, while DCs receive these antigens and then migrate to the draining lymph node to present them to T cells.

3. Mechanisms of evasion of bacterial recognition

DCs are alerted of the presence of pathogens via the binding of microbe-associated molecular patterns (MAMPs) to specialized pattern recognition receptors (PRR). PRRs are a family of receptors that include Toll-like receptors (TLR), nucleotide-binding site and leucine-rich repeat containing receptors (NLR) and retinoic acid inducible gene-I (RIG)-like receptors (RLR) (for a comprehensive review see [22]). The binding of MAMPs to PRR results in DC activation and release of immune modulators. Many pathogens can interfere with microbial pattern recognition either by modulating the expression of PRRs or their subsequent signaling pathways, reviewed in this issue by Sellge and Kufer.

The best characterized PRR ligands are TLR ligands, of which the most known is lipopolysaccharide (LPS). LPS binds MD2 and TLR4 and induces a cascade of events leading to DC maturation and release of inflammatory cytokines. Some pathogens such as *Brucella abortus* avoid immune cell recognition via displaying an LPS with a different core structure that lacks a clear pathogen-associated molecular pattern and escapes TLR recognition [23]. *Brucella* mutants in the *wad*C gene have a disrupted LPS core, but retain the lipid A moiety and O-polysaccharide and become attenuated. This core-modified LPS is now recognized by MD2/TLR4 and bacteria readily induce DC maturation and cytokine production [23]. Along the same line, *Coxiella burnetii* diplays different chemotypes of LPS. None of three virulent strains of *C. burnetii* (Nine Mile Phase I, S or Priscilla) which differ in LPS chemical structure, induced significant DC maturation in terms of cell surface markers expression or IL-12 production, whether this is related to the mutated LPS is not known [24].

Various TLRs are expressed primarily on certain DC subsets. TLR9 for instance is expressed mostly on human plasmacytoid DCs, which are pivotal cells in the response to viruses as they release great amount of type I Interferons (IFNs) [25], also reviewed by Coccia and Battistini in this issue. TLR9 is a sensor of bacterial and viral DNA motifs. TLR9 engagement leads to the activation of IRF7 transcription factor and type I IFN production [26]. Hepatitis B virus (HBV) particles are efficiently internalized but do not induce type I IFN production. After internalization HBV particles inhibit transcriptional activity of TLR9 and subsequent IFN-α production by blocking the IRF7 activity, via a mechanism that is independent on HBsAg. This activity is dependent on neutralizing CpG motifs present in the HBV genome [27].

Some TLRs like TLR2 signal as heterodimeric receptors. TLR2 can bind to TLR6 or TLR1 for transducing intracellular signals. *Yersinia pestis* virulence factor LcrV hijackes the TLR2 capacity to bind TLR6 to induce tolerogenic DCs that drive the differentiation of IL-10 producing T cells [28]. By contrast if TLR2 would couple with TLR1 the outcome would have been inflammatory and immunogenic.

Mycobacterium tuberculosis (Mtb) lipoprotein LprA has been shown to be a TLR2 agonist with different activities in DCs or macrophages. While in DCs it induces their activation, in macrophages LprA impacts on IFN-γ induced MHC class II up-regulation and antigen presentation [29]. Whether LprA is recognized by different heterodimeric receptors of TLR2 in the two cell types remains to be established.

PRRs can be located on the cell surface or intracellularly, in the cytoplasm or vesicular structures. Intracellular PRRs are devoted to the recognition of MAMPs associated to intracellular pathogens. RIG-I, for instance, is a sensor of viral-associated RNA and leads to the production of potent anti-viral mediators such as type I Interferons (IFN-α and IFN-β) [30] also reviewed by Coccia and Battistini in this issue. Some RNA viruses, but not DNA viruses or bacteria, can modulate the expression of lectins such as Sialic acid-binding immunoglobulin-type lectins (Siglec)-G in macrophages. This induces the recruitment of SHP2 and c-Cbl (an E3 ubiquitin ligase) to RIG-I for its subsequent degradation [31]. Interestingly, Siglec-G up-regulation is induced after binding of viral RNA to RIG-I thus creating a negative feedback loop and blocking the production of type I IFNs.

TLRs are involved in the recognition of both intracellular and extracellular pathogens, depending on the TLR member that is engaged. After TLR signaling, several adaptors are involved in the signal transduction cascade. The most used is MyD88. The tir-containing protein BtpB is a recently identified *Brucella* effector that carries a Toll/interleukin-1 receptor (TIR) homology domain that is translocated into the host cell and interferes with TLR signaling probably via interaction with MyD88 [32]. This affects DC activation and the initiation of immunity to *Brucella*.

One intracellular outcome of MAMP recognition is the activation of the inflammasome. Several MAMPs can trigger the inflammasome pathway, including bacterial DNA that activates the interferon inducible protein Absent in Melanoma (AIM)2 and leads to IL-1β release. Virulent strains of *Mtb* release DNA via the type VII (ESX)-1 secretion system. Thus it was thought that *Mtb* would induce AIM2 activation, however while non-virulent *M. smegmatis* induces AIM2 activation via an IFN-β dependent mechanism, virulent *Mtb* H37Rv does not. Interestingly the inhibition of AIM2 is dependent on the ESX-1 secretion system [33]. Haemolytic pneumolysin from *Streptococcus pneumonia* also inhibits the activation of the inflammasome and DC maturation while promoting DC apoptosis [27].

4. Exploitation of APC surface receptors

Chemokine receptors are used by APCs to migrate in response to chemokine gradients. CCR5 is a common chemokine