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Microbe- and danger-induced inflammation☆

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ABSTRACT

The ability of the immune system to give rise to an effective response against pathogens while maintaining tolerance towards self-tissues has always been an object of keen interest for immunologist. Over the years, different theories have been proposed to explain if and how the immune system is able to discriminate between self and non-self, including the Infectious Non-self theory from Charles Janeway and Polly Matzinger's Danger theory. Nowadays we know Janeway's theory is largely true, however the immune system does respond to injured, stressed and necrotic cells releasing danger signals (DAMPs) with a potent inflammatory response. To avoid unwanted prolonged autoimmune reactions, though, danger-induced inflammation should be tightly regulated. In the present review we discuss how prototypic DAMPs are able to induce inflammation and the peculiarity of danger-induced inflammation, as opposed to a complete immune response to fight pathogen invasions.

1. Introduction

The capacity of the immune system to activate strong adaptive responses against pathogen-derived antigens while maintaining tolerance towards self-molecules or harmless substances has always been of keen interest for immunologists.

The first model proposed to explain this phenomenon, was theorized by Burnet back in 1959 (Burnet, 1959). It suggested that each lymphocyte expresses a specific receptor that recognizes foreign antigens and self-reactive lymphocytes are deleted early in life. Medawar and colleagues' (Billingham et al., 1953) brought experimental support to this model by successfully transplanting skin grafts in adult mice that had been injected with donor cells as babies. However, it was soon evident that the simple introduction of a foreign antigen to the body was not sufficient to elicit a proper T cell response and that together with antigen recognition (signal 1), T cells need to be provided with a second signal in the form of a costimulation (Lafferty and Cunningham, 1975) to be conferred by professional antigen presenting cells (APCs) such as dendritic cells (DCs) (Banchereau and Steinman, 1998).

In 1989 Charles Janeway introduced the Infectious Non-self (INS) theory of immunity, stating that the innate immune system acted as a sensor of pathogenic invasions and that APCs used conserved innate sensors to discriminate between infectious non-self and non-infectious self. He postulated that APCs must express evolutionary conserved pattern recognition receptors able to recognize essential and conserved structures of a pathogen, so called PAMPs (pathogen associated molecular patterns) and suggested that APCs where quiescent until they encountered a pathogen able to activate them through a PAMP/PRR interaction; this then induced the ability to produce costimulatory signals, process antigens and present them to antigen specific T cells (Janeway, 1989, 1992). Though this theory was fascinating, it could not explain many observed immune reactions where non-self or infectious non-self stimuli where absent, such as tolerance to the intestinal microbiota, reactions against tumours, responses to trauma or injuries, and autoimmune reactions.

In an attempt to theorize a model consistent with these observations, Polly Matzinger introduced, before the discovery of PRRs, the Danger Theory (Matzinger, 1994). In contrast to Janeway's concept of infectious non-self, Polly Matzinger proposed that the immune system was alerted by the recognition of the damage induced by a pathogen rather than by the pathogen itself. She theorized the presence of conserved, abundant and ubiquitously expressed self-molecules that are normally hidden within the cells and released by distressed, injured or necrotic cells. These molecules, called damage associated molecular patterns (DAMPs) would be recognized by APCs via conserved receptors and mediate the activation of APCs to produce costimulatory signals and start an adaptive response to damage.

Nowadays, we know that Janeway's theory is largely true but not every immune reaction can be explained by it. In particular, the danger theory can complement the INS model in the case

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of inflammatory reactions to distressed or necrotic cells. Inflammation can be beneficial in case of trauma or necrosis: swelling and increased interstitial pressure can prevent the spreading of noxious substances, while phagocytic leukocytes can help to clear debris and dead cells, and to end the inflammatory process triggering the repair process. However responses to cell death or stress should be tightly regulated in order not to elicit unwanted adaptive responses that could lead to autoimmunity. Here we discuss how typical DAMPs induce inflammation and the peculiarity of danger-induced inflammation, as opposed to a complete immune response to pathogen invasion.

2. PAMP associated responses: the example of TLRs

When Janeway's theory was formulated, some molecules involved in innate recognition of pathogens where already known. They where, however, either soluble factors, like mannan binding lectin and pentraxins, or expressed only by subsets of innate immune cells, like the MARCO receptor (Medzhitov, 2009). The prototypic PRR they where looking for should have been a surface receptor expressed by all APCs, and should have been able to trigger an intracellular signalling pathway resulting in the upregulation of costimulatory molecules. It was also known that the response to LPS involved the transcription factor NF-κB and that the NF-κB signalling pathway could be activated by interleukin (IL)-1 receptor via an intracellular domain called TIR, which was common to IL-1R, the drosophila Toll and a resistance protein from tobacco. Janeway and colleagues where, therefore, fishing for a receptor with an extracellular domain that was able to bind microbial antigens and an intracellular domain able to induce NF-κB, possibly via a TIR domain. It was indeed identified a sequence that was homologue to drosophila Toll, harbouring the TIR domain (Nomura et al., 1994). The sequence was identified in Janeway's lab but they could not find a microbial ligand. The fact that drosophila Toll was known to bind an endogenous protein, then, dampened their hopes. When Jules Hoffmann discovered the essential role of drosophila Toll in antifungal defence (Lemaitre et al., 1996), their hopes where revived and they suggested that the newly discovered human Toll (now named TLR4) was involved in microbial recognition (Medzhitov et al., 1997). The microbial ligand was not known, at the time, and it was postulated that microbial recognition was dependent on a proteolytic cascade, similar to the one observed in drosophila (Medzhitov, 2009). Later on, it was found that the mutation that rendered C3H/HeJ mice unresponsive to LPS mapped in the TLR4 locus, giving the first genetic evidence of TLR4 involvement in LPS recognition (Poltorak, 1998). Since then, many other PRR have been identified. To date, 10 members of the toll like receptors family have been identified in human and 13 in mouse and most of their microbial ligands have been identified. TLRs can be considered prototypic PRRs but over the years other classes of PRRs have been identified including C-type lectin receptors, such as DECTIN-1, involved in fungal recognition (Brown and Gordon, 2001), intracellular receptors, like RIG-I, involved in the viral response and NOD like receptors, cytosolic sensors able to induce inflammasome activation and IL-1 secretion (Strowig et al., 2012).

TLRs share common features both in terms of structure and in terms of intracellular signalling. They are transmembrane proteins with an extracellular domain containing multiple leucine-rich repeats (LRRs) organized in a typical horseshoe-shaped folding. Upon binding to their ligands, TLRs are able to form homo or hetero-dimers and to recruit adaptor molecules to the intracellular TIR domains that in turn activate pro-inflammatory intracellular pathways. The different members of the TLR family, though, are able to bind a very heterogeneous ensemble of microbial products. For instance, together with TLR1 and TLR6, TLR2 is able to recognize lipoproteins from Gram-positive bacteria, TLR4 recognizes LPS, TLR5 recognizes flagellin, and TLR9 recognizes bacterial DNA. Other TLRs such as TLR3, 7 and 8 are able to recognize virus-associated single or double stranded RNA (Kawai and Akira, 2006).

If TLRs can be considered prototypic PRRs, TLR4 recapitulates many of the common features of TLRs. Upon PAMP recognition TLRs activate common intracellular inflammatory pathways, culminating in the activation of the transcription factors NF-κB and AP-1. TLR4 in fact, along with the adaptor protein MD2 and the co-receptor CD14, upon binding to its ligand LPS, can dimerize, recruit the adaptor protein TIRAP to its TIR domain and trigger MyD88 recruitment. MyD88 in turn, is able, trough the adaptor molecule TRAF6 and IRAK4, to trigger the translocation of the transcription factor NF-κB to the nucleus, and to activate the MAPK cascade that culminates with the phosphorylation of AP-1 and its translocation to the nucleus. Together these transcription factors are able to initiate DC maturation and to induce pro-inflammatory cytokine production (Kawai and Akira, 2006).

After the LPS binding to the TLR4 receptor complex, and once the Myd88 pathway is activated, the complex is endocytozed in a CD14 dependent manner (Zanoni et al., 2011) and activates another signalling pathway by recruiting to the endosome the adaptor protein TRAM that in turn recruits TRIF and triggers the activation of IRF3. IRF3, then, associates with NF-κB and AP-1 to induce the production of type 1 interferons. The TLR4 co-receptor CD14 possesses autonomous signalling capacities in DCs and it is able to induce Src-family kinases and phospholipase C gamma-2 (PLCγ2) activation, influx of extracellular calcium and calcineurin-dependent nuclear NFAT translocation (Zanoni et al., 2009). The activation of the NFAT pathway in DCs is required to control DC life cycle (Zanoni et al., 2009) and to regulate IL-2 and lipidic pro-inflammatory mediators production (Zanoni et al., 2012). Other PRRs such as DECTIN-1 can also trigger NFAT activation and IL-2 production (Goodridge et al., 2007).

Most of the TLRs are able to induce the conserved inflammatory pathways involving NF-κB and AP-1 through MyD88. TLR4 and TLR3 induces the TRIF pathway and activate IRF-3 while TLR7/8 and TLR9 induce type I interferon production via MyD88 and IRF-7.

A microbial invasion, then, is able to trigger a very potent pro-inflammatory response and, more importantly, fully activates DCs to efficiently induce a strong adaptive response enhancing the ability of DCs to deliver signal 1 (TCR engagement), signal 2 (costimulation) and signal 3 (pro-inflammatory cytokines) to naïve T cells (Fig. 1).

The efficiency of presenting phagocytized antigens is, indeed, dependent on the presence of TLR ligands within the phagosome, thus the efficiency of processing and presenting microbial antigens to T cells is dramatically increased in the presence of TLR ligands (signal 1) (Blander and Medzhitov, 2006). Moreover, TLR engagement and NF-κB activation upregulate the costimulation on the surface of DCs providing the so-called signal 2 and triggering T cell activation (Schnare et al., 2001).

The third signal needed by T cells for optimal activation is represented by pro-inflammatory cytokines produced by DCs. The nature of the T cell response is profoundly affected by the cytokine milieu in which a T cell is activated but pro-inflammatory cytokines have also the fundamental function to release effector T cells from Treg suppression. In fact, IL-6 produced by DCs after TLR activation have been shown to be fundamental to release effector T cells from regulatory T cells (Treg) suppression (Pasare and Medzhitov, 2003) and persistent TLR stimulation is needed for reversal of Treg mediated tolerance (Yang et al., 2004). TLR8 ligands can also directly stimulate Tregs inhibiting their suppressor activity (Peng et al., 2005). Recently it has been demonstrated that T cell specific ablation of MyD88 impairs the ability of T cells to overcome Treg