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Modulation of dendritic cell antigen presentation by pathogens, tissue damage and secondary inflammatory signals

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Antigen presentation by dendritic cells (DC) is regulated directly by pathogen-associated or cell death-associated cues, or indirectly by immunomodulatory molecules produced during infection or tissue damage. DC modulation by direct encounter of pathogen-associated compounds has been thoroughly studied; the effects of molecules associated with cell death are less well characterized; modulation by secondary signals remain poorly understood. In this review we describe recent studies on the role of these three categories of immunomodulatory compounds on DC. We conclude that characterization of the role of secondary immunomodulators is an area in dare need of further study. The outcomes of this endeavor will be new opportunities for the development of better vaccines and compounds applicable to the therapeutic immunomodulation of DC function.

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Dendritic cells (DCs) are a fundamental component of the immune system. They can detect virtually any pathogen, multiple forms of tissue damage and secondary mediators of inflammation. They are also the predominant antigen presenting cells for the maintenance of T cell tolerance and the initiation and regulation of T cell-dependent immune responses. By combining the capacity to detect environmental changes, and to communicate with T cells, DCs bridge the innate and adaptive arms of the immune system.

DC precursors constantly leave the bone marrow and seed peripheral tissues and secondary lymphoid organs, where they develop into *immature* DC [1]. In this state of differentiation DC are highly endocytic and survey their environment. Immature DC express relatively low levels of two types of molecules required for activation of naive T cells, namely Major Histocompatibility Complex (MHC) molecules, which present antigenic peptides recognized by T cell receptors (the so-called *signal 1*), and co-stimulatory molecules required for T cell activation (e.g. CD40, CD86, *signal 2*). In the absence of infection, tissue damage or inflammation, the DC that develop in secondary lymphoid organs die in the immature state, with a turn-over rate of less than a week [1]. The DC that develop in peripheral tissues constitutively migrate to lymphoid organs, where they acquire a so-called *mature* phenotype characterized by high surface expression of MHC and co-stimulatory molecules [2]. Migratory DC have a more variable but also fast turn-over rate [1]. The term *steady-state DC* is often used to refer to the DC present in the periphery and lymphoid organs in the absence of overt infection or inflammation. Steady-state DC do not secrete cytokines required for immunogenic T cell activation (the so-called called *signal 3*) and it is widely accepted that if T cells recognize antigens presented by these DCs they die, lose the capacity to become effector (immunogenic) T cells, or become regulatory T cells dedicated to dampening rather than promoting immune responses [3]. In other words, steady-state DC are *tolerogenic*. Detection of molecular cues associated with infection, tissue damage or inflammation has been generally thought to induce DC differentiation into *immunogenic* mature DC. In this review we describe recent work suggesting that this view is too simplistic, as the encounter of different types of activating stimuli can lead to generation of mature DCs with distinct capabilities. Moreover, there is evidence that the effects of infection and inflammation can extend for longer than anticipated and affect the life cycle or function of new DC produced after resolution of these events.

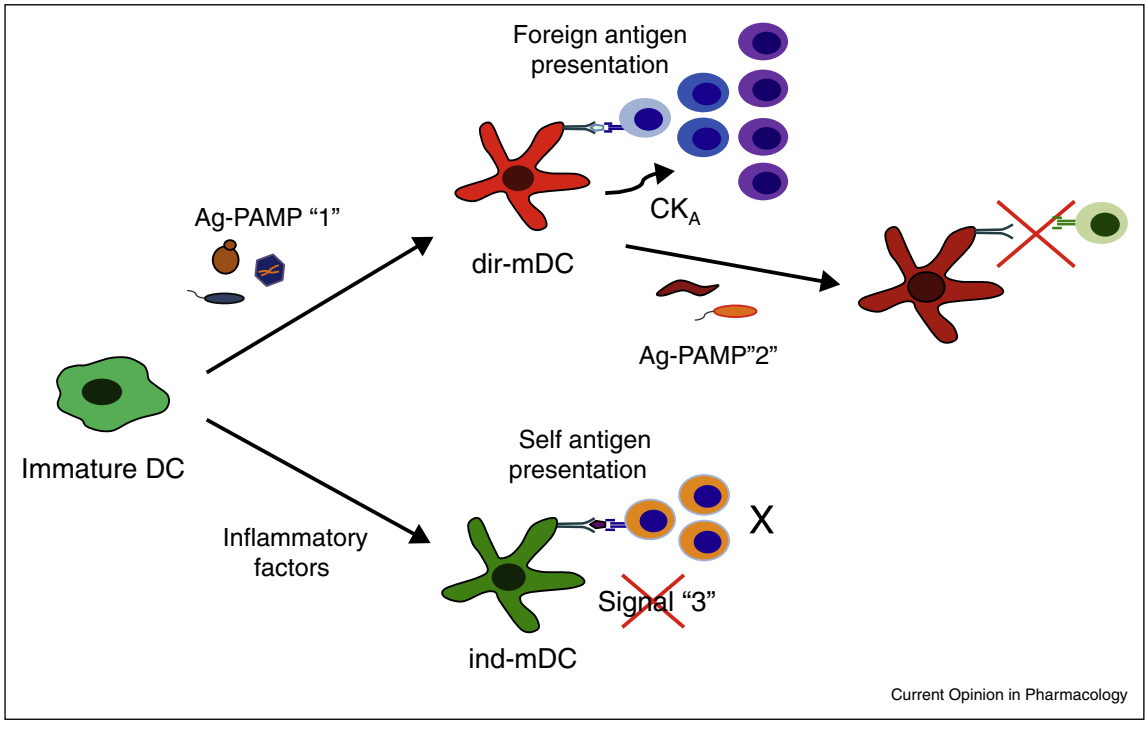
DC modulation by pathogen-associated and danger-associated molecular patterns

The best-studied mechanism of DC activation is through pattern-recognition receptors such as Toll-like receptors and the cytosolic sensors of the RIG and NOD families, which recognize lipopolysaccharide, non-eukaryotic nucleic acids and other pathogen associated molecular patterns (PAMPs). DC activated by PAMPs acquire a mature phenotype and in addition secrete signal 3 cytokines, so they are immunogenic (Figure 1). The specific suite of cytokines induced by each PAMP is tailored to promote the most adequate type of immune response to fight the agent expressing the PAMP. The process of DC activation by PAMPs has been reviewed elsewhere [4,5].

The second major family of DC modulators are the danger-associated molecular patterns (DAMPs) [6]. These are compounds that are normally only found inside cells but are released when cells undergo 'violent' death caused by infection or tissue damage (necrosis), as opposed to the non-activating cell death program that cells undergo when they reach the end of their life cycle (apoptosis). The DAMPs are not as finely characterized as the PAMPs, and neither are their receptors and functional consequences of their engagement [7]. Some examples of DAMPs are ureate, ATP, high-mobility group box 1 (HMGB1) protein or mitochondrial DNA [6]. Many are recognized by the same receptors that detect PAMPs, so it is likely that the DC modulatory activity of these two groups of compounds overlaps [7]. For simplicity, in the rest of this review we will refer to DC activated by detection of PAMPs or DAMPs as 'directly matured DC (dir-mDC)' to distinguish them from those that mature in response to secondary inflammatory signals (see below and Figure 1).

A distinctive feature of dir-mDC is that while they are highly adept at presenting a long-lived 'snapshot' of antigens acquired at the time of activation, they also lose their ability to present newly encountered antigens [8] (Figure 1). There is one exception to this general rule: antigens captured via surface molecules are efficiently presented by dir-mDC [9•,10•]. Although it is unclear whether this property contributes to natural initiation of T cell immunity, it might be exploited for clinical purposes by using artificial constructs to target antigens to surface molecules on dir-mDC [11]. Down-regulation of new antigen presentation by dir-mDC is not deleterious

Figure 1



Functional properties of directly versus indirectly activated DC. Dendritic cells can be activated directly by encounter of pathogen associated molecular patterns (PAMP), or indirectly by inflammatory mediators produced by other hematopoietic cells. Upper path: direct encounter of a pathogen (Ag-PAMP '1') activates DC, which mature (dir-mDC). The dir-mDC present the antigen to elicit activation and expansion of specific T cells, and also produce 'signal 3' cytokines which induce the differentiation of the expanded T cells. Dir-mDC down-regulate the synthesis and turn-over of MHC-II molecules, so they have a low capacity to respond to, and present, subsequently encountered antigens (Ag-PAMP '2'). Lower path: DC indirectly activated by inflammatory signals also mature (ind-mDC). As they have not captured foreign antigen, they can only present self antigens and induce proliferation of self T cells, but they do not induce full differentiation of the T cells due to a lack of 'signal 3' cytokine production.