Molecular Immunology 55 (2013) 175–178

Contents lists available at SciVerse ScienceDirect

Molecular Immunology

journal homepage: www.elsevier.com/locate/molimm

Review

Consequences of direct and indirect activation of dendritic cells on antigen presentation: Functional implications and clinical considerations☆

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ARTICLE INFO

Article history:
Received 16 October 2012
Received in revised form 24 October 2012
Accepted 24 October 2012
Available online 27 November 2012

Keywords:
Dendritic cell
Pathogen
Antigen Presentation

ABSTRACT

The antigen presentation properties of Dendritic cells (DC) are key factors in the initiation and modulation of immune responses. The mechanisms involved in the regulation of MHC II antigen presentation in DC have been thoroughly investigated. Here, we will summarize recent advances in the field, focusing on how DC regulate antigen presentation during and after maturation, and its functional implications. We will also discuss future perspectives and clinical considerations.

1. Introduction

Dendritic cells (DC) are distributed in peripheral tissues and lymphoid organs, where they are found in an *immature* state dedicated to sample their environment by a variety of endocytic mechanisms. They also express a wide range of receptors for pathogen products (e.g. Toll-Like Receptors (TLR)). Upon binding their ligands, these receptors activate the DC, triggering a differentiation program that culminates in the acquisition of a *mature* phenotype characterized by high surface expression of MHC class II (MHC II) and T cell co-stimulatory molecules (e.g. CD80, CD86 and CD40). A defining property of mature DC is that they can present with high efficiency and for prolonged periods antigens captured at the time of pathogen encounter, but they lose the capacity to present subsequently encountered antigens (Villadangos et al., 2005). This general model has been challenged in recent years by studies that show that DC that mature in response to pathogen products retain their capacity to present at least some form of antigen (Drutman and Trombetta, 2010; Platt et al., 2010). Furthermore, it is known that DC can also mature in response to inflammatory cytokines released during infections, and it seems that such DC retain their antigen presentation function largely intact (Simmons et al., 2012).

Characterization of the antigen presentation properties of mature DC is important for three reasons. Firstly, their function has traditionally been considered to induce immunity or tolerance toward antigens captured at the time and site of activation, but this notion may have to be revisited in light of the new advances. Secondly, the timing of DC activation after encounter with activating compounds (adjuvants) and antigen, and the subsequent changes induced by DC maturation, can dramatically affect the outcome of vaccination. Thirdly, certain pathologies such as sepsis, malaria infection, multiple trauma and severe burns induce systemic DC maturation and, as we have proposed, this may cause depletion of DC capable of presenting new antigens and contribute to the immunosuppression that accompanies these conditions (Njie et al., 2009; Villadangos et al., 2005; Young et al., 2007). Here we will summarize the current status of this area and possible future trends.

2. Current status

Work carried out by ourselves and others has contributed to define the mechanisms involved in regulation of MHC II antigen presentation in DC (Villadangos et al., 2005). Immature DC constitutively capture extracellular material by macropinocytosis, phagocytosis and receptor-mediated endocytosis. Extracellular proteins, along with components produced by the DC themselves, are degraded in endosomal compartments and presented on the cell surface as antigenic peptides bound to MHC II molecules. These MHC II-peptide complexes have a short half-life (hours) because they are ubiquitinated by the E3 ligase MARCH 1, which induces their delivery to lysosomal compartments, where they are degraded. In DC stimulated by pathogen encounter, macropinocytosis and phagocytosis are up-regulated to promote engulfment of

☆ This article belongs to Special Issue on Antigen Processing and Presentation.

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0161-5890/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.molimm.2012.10.034

the pathogen. Synthesis of MHC II is also transiently up-regulated, causing increased formation of new peptide-loaded complexes, some of which carry peptides derived from pathogen antigens. These complexes gradually accumulate on the surface of the DC undergoing maturation because MARCH 1 expression, and therefore MHC II ubiquitination and turn-over, decreases. Subsequently, synthesis of new MHC II molecules is nearly shut-down, as does macropinocytosis and phagocytosis. The result of these concerted changes is the accumulation of long-lived MHC II-peptide complexes on the surface of mature DC. These changes are specific to the MHC II pathway because synthesis and turn-over of MHC I molecules are up-regulated during DC maturation.

While mature DC are very efficient at presenting antigens captured at the time of activation, their capacity to present subsequently encountered antigens via MHC II is severely reduced. Down-regulation of macropinocytosis and phagocytosis impairs their presentation of soluble protein vaccines and particulate or cell-associated antigens (Bouvier et al., 2011; Wilson et al., 2006; Young et al., 2007). But even antigens that are still captured by mature DC by fluid-phase pinocytosis, or that do not need to be captured from the extracellular environment because they are synthesized by the DC itself, are poorly presented (Young et al., 2007). This is because the major source of MHC II molecules for antigen presentation is newly synthesized (ten Broeke et al., 2011), and mature DC synthesize little MHC II. Indeed, DC engineered to retain MHC II synthesis in their mature state are capable of presenting antigens captured post-activation by fluid-phase pinocytosis (our unpublished results).

There is a category of antigens that are still well presented by mature DC, namely those internalized by Fc receptors or putative antigen receptors such as CD205 ((Platt et al., 2010) and our unpublished results). In this case the source of MHC II molecules that present the antigenic peptides are pre-existing MHC II-peptide complexes that traffic to endosomal compartments, replace the previously bound peptide with a new one, and recycle back to the cell surface. This implies that once they have reached the mature state, the repertoire of peptides derived from newly encountered antigens that DC can present is limited to those derived from antigens captured by endocytic receptors and that have sufficient affinity to displace pre-existing peptides from the binding site of recycled MHC II molecules.

Studies performed by different groups on DC activated in vitro with TLR agonists generally agree with the conclusions described above, but the studies that have addressed this same question in vivo are more controversial. Our own assessments showed that DC activated in vivo with TLR ligands underwent similar changes to

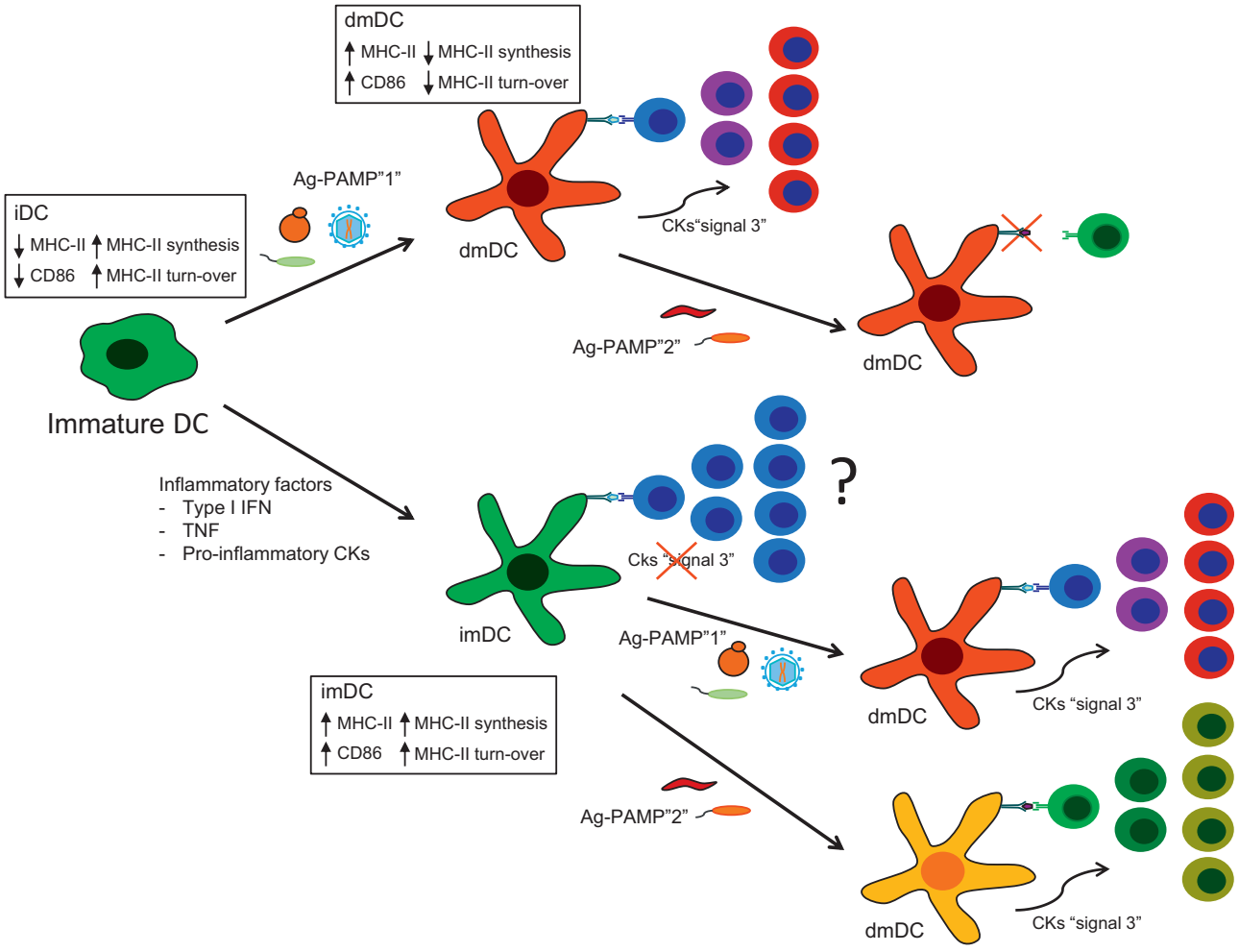

Fig. 1. Functional properties of directly vs. indirectly activated DC. Dendritic cells can be activated directly by encounter of pathogen associated molecular patterns (PAMP), or indirectly by inflammatory mediators produced by other hematopoietic cells. DC that matured by direct contact with PAMPS (dmDC) show increased surface levels of MHC-II and T cell co-stimulatory molecules, promote the expansion of specific T cells and produce "signal 3" cytokines which induce the differentiation of expanded T cells. The dmDC down-regulate synthesis and turn-over of MHC-II molecules and have a low capacity to respond to, and present subsequently encountered antigens. On the other hand, indirectly activated mature DC (imDC) also show increased surface levels of MHC-II and co-stimulatory molecules and can induce proliferation of T cells, but do not induce differentiation of T cells due to a lack of "signal 3" cytokine production. The imDC retain their capacity to respond to, and present antigens from, subsequently encountered pathogens, due to sustained MHC-II synthesis and turn-over.