Preface—Dendritic cells: Master regulators of innate and adaptive immunity

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Dendritic cells (DCs) are a population of myeloid cells that play a key role in the initiation of adaptive immune responses, a core immunological activity that reflects their proficiency at presenting extracellular antigens to naïve T cells and earned them the name of "sentinels of the immune system" (Reis e Sousa, 2006). These professional antigen-presenting cells were originally discovered by the Canadian physician Ralph Steinman in 1973 (Steinman, 1991; Steinman and Cohn, 1973), who was the first to observe cells with a peculiar tree-like morphology in mouse peripheral lymphoid organs and named them dendritic cells after the Greek word *dendreon* (tree). A few years later, Steinman and colleagues demonstrated that DCs are potent inducers of the so-called "mixed leukocyte reaction" (a rather outdated term referring to the experimental assessment of T cell priming) in mice (Steinman and Witmer, 1978) as they highlighted multiple phenotypic and functional properties of DCs (Nussenzweig and Steinman, 1982; Steinman, 1991). In 2011, Ralph Steinman was awarded the Nobel Prize in Physiology or Medicine "for his discovery of the dendritic cell and its role in adaptive immunity," jointly with the American immunologist Bruce Beutler and the Luxembourger biologist Jules Hoffmann "for their discoveries concerning the activation of innate immunity" (Lemaitre et al., 1996; Poltorak et al., 1998).

The phenotypic and functional heterogeneity of DCs became apparent early after their discovery (Maldonado-Lopez et al., 1999; Pulendran et al., 1999; Vremec et al., 1992). Indeed, despite a shared ability for antigen uptake, processing and presentation to naïve T cells, DCs exhibit a wide spectrum of phenotypic and functional properties that—coupled to their anatomical location—have a major impact on their capacity to regulate immune responses (Alcantara-Hernandez et al., 2017; Hashimoto et al., 2011). Both human and mouse DCs can be broadly classified into two major lineages

based on morphology: myeloid DCs (mDCs), also known as classical or conventional DCs (cDCs), which (prior to activation) resemble circulating monocytes; and plasmacytoid DCs (pDCs), the latter of which display some morphological resemblance to plasma cells (Merad et al., 2013). Two other subsets of DCs have been described: monocyte-derived (or inflammatory) DCs, which are believe to originate from $CD16^+$ monocytes; and Langerhans cells (LCs), a skin-resident population of DCs with potent immunosuppressive activity (Collin and Bigley, 2018; Price et al., 2015). cDCs originate from a common myeloid precursor and can be classified into two phenotypically distinct subsets: cDC1, which express CD8α or CD103 in mice, or CD141 in humans; and cDC2, which express CD11b in mice, or CD1c in humans. pDCs have been suggested to originate from a poorly defined lymphoid precursor and are characterized by the co-expression of CD45R/B220 and Ly-6C in mice or CD123 and CD304 in humans. DCs have also been classified based on the differential expression of key transcription factors such as basic leucine zipper transcription factor ATF-like 3 (BATF3), which is known for its role in the development of $CD8\alpha^+$ DCs in lymphoid tissues and $CD103^+CD11b^-$ DCs in the periphery (Collin and Bigley, 2018; Hildner et al., 2008; Schlitzer et al., 2013). Recently, the use of high-dimensional analysis techniques (e.g., single-cell RNA-sequencing, mass cytometry) has opened new avenues for studying the complexity of DCs, casting doubts on the precision of the aforementioned taxonomy (See et al., 2017; Villani et al., 2017).

The ability of DCs to induce robust immune responses is highly dependent on their maturation status (Truxova et al., 2018). Through the expression of pattern recognition receptors such as Toll-like receptors (TLRs), C-type lectin receptors, Nod-like receptors (NLRs) and others (Akira et al., 2006; Galluzzi et al., 2018a; Takeuchi and Akira, 2010), immature DCs can indeed decode microenvironmental signals of danger, including microbe-associated molecular patterns (MAMPs) as well as damage-associated molecular patterns (DAMPs), and undergo a phenotypic and functional shift that underlies their ultimate immunological activity (Galluzzi et al., 2017). Thus, while immature DCs display intense endocytic and phagocytic capacity but are poor at antigen presentation, their mature counterparts express high amounts of MHC Class II molecules, co-stimulatory molecules (e.g., CD80, CD86, CD40) and chemokine receptors (e.g., CCR7) allowing them to migrate to lymphoid organs and stimulate naïve T cells (Banchereau et al., 2000; Reis e Sousa, 2006). Importantly, depending on subset, phenotype, and maturation status, DCs may

induce tolerogenic or immunogenic responses downstream of the polarization of different $CD4^+$ helper T cell populations (e.g., T_H1, T_H2, T_H9, T_H17, T_H22) or the functional interaction with $CD8^+$ cytotoxic T lymphocytes (CTLs) or $CD4^+CD25^+FOXP3^+$ regulatory T (T_{REG}) cells (Devi and Anandasabapathy, 2017; Tanchot et al., 2013). The precise mechanisms whereby different DCs subsets orchestrate T-cell responses remain to be fully elucidated.

From a functional perspective, the cDC1 subset is specialized at cross-presenting microenvironmental antigens on MHC Class I molecules to $CD8^+$ T cells in the context of type I interferon (IFN) secretion (Bachem et al., 2010; den Haan et al., 2000), an activity that is critical for anticancer immune responses (Galluzzi et al., 2018b; Zitvogel et al., 2015). Conversely, cDCs subset efficiently presents exogenous antigens on MHC Class II molecules to $CD4^+$ T cells (Collin and Bigley, 2018; Desch et al., 2014; Segura and Amigorena, 2015). However, cDC2 DCs are more heterogeneous than their cDC1 counterparts and some $CD8\alpha^-$ DCs have been shown to engage in cross-presentation upon activation (Collin and Bigley, 2018; Desch et al., 2014; Segura and Amigorena, 2015). Finally, pDCs are extraordinarily potent at producing type I and type III IFNs upon viral infection, de facto constituting a major player in innate antiviral immunity (Dubois et al., 2019; McNab et al., 2015; Swiecki and Colonna, 2015). Multiple DC subtypes can also interact with natural killer (NK) cells, a cross-talk that can result in the pruning of the DC compartment and mutual activation (Barry et al., 2018; Ferlazzo and Moretta, 2014). Of note, the immunomodulatory functions of DCs are not only mediated by cell-to-cell interaction and cytokine secretion but also by the release of extracellular vesicles (Pitt et al., 2014).

Despite their fundamental role in early responses against viral pathogens, DCs can also contribute to the etiology of various human disorders. For instance, human immunodeficiency virus type 1 (HIV-1) highjacks DC functions in support of viral replication, distal dissemination, and cell-to-cell transmission (Wacleche et al., 2018). Moreover, some DCs subsets express high levels of the immunosuppressive enzyme indoleamine 2,3-dioxygenase 1 (IDO1), which can be detrimental effects in some pathophysiological settings including chronic infections and cancer (Harden and Egilmez, 2012). Finally, Langerhans cell histiocytosis is a rare myeloproliferative disorder mostly affecting children that is driven by uncontrolled LC proliferation (Allen et al., 2018; Chakraborty et al., 2003).

Not surprisingly, DCs have attracted considerable attention as potential targets for the development of novel therapeutic interventions against a

variety of human disorders. On the one hand, infusion of tolerogenic DCs as induced by specific pharmacological agents, growth factors, or cytokines may be beneficial in the context of allergic disorders, autoimmune diseases, and transplant rejection. Conversely, vaccines based on autologous DCs loaded with tumor-associated antigens in the context of robust immunostimulatory signals have demonstrate significant anticancer activity in both preclinical and clinical settings (Garg et al., 2017; Kantoff et al., 2010; Medler et al., 2019; Palucka and Banchereau, 2012; Tacken et al., 2007; Vacchelli et al., 2013). Intriguingly, one therapeutic option for prostate carcinoma approved by the U.S. Food and Drug Administration (FDA) consists in a DC-enriched mixture of autologous myeloid cells engineered to express a tumor-associated antigen fused to colony stimulating factor 1 (CSF1, best known as GM-CSF) (Cheever and Higano, 2011).

In *Immunobiology of dendritic cells* (a special issue of the *International Review of Cell and Molecular Biology* series) worldwide recognized experts in the field provide an overview of ontological, biological, and functional DCs features in the context of human pathophysiology. Each of the chapters of *Immunobiology of dendritic cells* critically discusses the key role of DCs at the interface between innate and adaptive immunity from a unique mechanistic or therapeutic perspective. The book (which consists of two parts, part A and part B) is equally addressed to expert researchers who may be interested in acquiring in-depth insights into the key role of DCs at the interface between innate and adaptive immunity, and to neophytes of this expanding field of translational investigation.

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Conflict of interest

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