

Preface

The understanding of the role of dendritic cells (DCs) in immune responses has come a long way since Steinmann and colleagues described these cells in 1972. Extensive research during the intervening period has provided a good understanding of the complexity of the DC system and its pivotal role in immunity. It is also now clearer how different subsets of DCs interact and regulate each other and how DC populations affect the function of other cells of the immune system. The improved understanding of their role in immune response has led to the idea that modulation of DC functions by, for example, pharmacological agents could be used as a potential therapeutic approach in some pathological conditions. The actual applicability and therapeutic potential of all these approaches is yet to be fully demonstrated but nonetheless, animal models of human diseases are proving to be very helpful in the evaluation of manipulated DCs as a new treatment in diseases like cancer, autoimmunity or asthma.

DCs are integral to the initiation and regulation of immune response (Banchereau et al. 2000). The outcome of antigen presentation by DCs is determined by their maturation status, which can be induced by their interaction with danger signals. To recognise a wide array of pathogen-associated molecular patterns (PAMP), DCs express a number of pattern recognition receptors (PRR) such as Toll-like receptors (TLRs) and C-type lectin receptors (CLR) that recognise structural components of pathogens and discriminate between self and non-self molecules. The distribution of PRRs by DCs is variable and differs between DC subsets, as reviewed in this issue of Handbook of Experimental Pharmacology. Following an encounter with pathogens, DCs stop sampling the microenvironment and become dedicated antigen presenting cells. These mature DCs migrate to the secondary lymphoid organs and present antigen to lymphocytes. The trafficking of DCs, in particular from skin and blood, has been reviewed in this volume. Mature DCs have a potent capacity to stimulate T cells, while immature DCs fail to fully activate T cells and can induce T cell tolerance through anergy, deletion or induction of Tregs (Bonifaz et al. 2002; Hawiger et al. 2001). More specifically, different DC subsets appear to have distinct effects on T cell behaviour. DCs are in fact a very heterogeneous population of cells. In mice there are at least six major subtypes of

DCs (reviewed by Pulendran et al. 2008). In the spleen and lymph nodes, DCs are characterised by the expression of CD11c and MHC class II. In the spleen there are three subsets: (1) CD11c^{high}CD8 α ⁺CD11b⁻DEC205⁺ (CD8 α ⁺ lymphoid DCs); (2) CD11c^{high}CD8 α ⁻CD11b⁺DEC205⁻ (CD8 α ⁻ myeloid DCs); (3) CD11c^{int}CD8 α ^{+/-}CD11b⁺B220⁺Gr-1^{+/-} (pDCs). However there is another way in which splenic DCs have been classified, based on the expression of CD4 and CD8 surface markers (Dudziak et al. 2007; Masson et al. 2008). Using these two markers, three populations of DCs can be discerned in the spleen: CD8 α ⁺CD4⁻ (CD8 α DCs) CD8 α ⁻CD4⁺, and CD8 α ⁻CD4⁻ (the last two defined as non CD8 α DCs). Furthermore, the CD8 α ⁺CD4⁻ DCs express the CD205 molecule, while the CD8 α ⁻CD4⁺ DCs express a high level of the C-type lectin inhibitory receptor-2 (DCIR2) which can be targeted by the antibody 33D1 (Dudziak et al. 2007). The percentages vary slightly, depending on the mouse strain. More recently, it has been shown that CD4⁻CD8 α ⁺ and CD4⁺CD8 α ⁻ DC stimulate CD8⁺ and CD4⁺ T cells respectively (Dudziak et al. 2007). These properties are related to differences in the MHC class I and MHC class II antigen presentation pathways (Dudziak et al. 2007). In the lymph nodes there are two additional subsets CD11c^{high}CD8 α ^{dull}DEC205^{high}Langerin⁺ (Langerhans cell-derived DCs-LCDCs) and CD11c^{high}CD8 α ⁻CD11b⁺DEC205⁺ (Dermal DCs). The LCDCs and the Dermal DCs in the lymph nodes are derived from skin (reviewed in this volume). All these subsets of DCs have different locations in the secondary lymphoid organs. The CD11c^{high}CD8 α ⁺ DCs are localised in the T cell area while the CD8 α ⁻ DCs are localised in the marginal zones of the spleen and the subcapsular sinuses of the lymph nodes. The CD8 α ⁺ DC subset secrete IL-12 while the CD8 α ⁻ produce mostly IL-10. While in vivo data suggests that CD8 α ⁺ DC stimulation of T cells generally promotes Th1 and CD8 α ⁻ DCs mainly promote a Th2 response, in vitro stimulation has shown that this division can be overcome (Maldonado-Lopez and Moser 2001). In this issue the role in particular of the anti-viral immune responses of different DCs subsets will be discussed. Apart from the three subsets of DCs present in the skin (LCDCs, Dermal DCs and pDCs) that migrate to the lymph nodes following activation, four different subsets of DCs have been described in three main locations in the intestine (Peyer's patches, lamina propria, and mesenteric LNs). These four subsets are similar to the subsets identified in the spleen with an additional marker, CCR6, to subdivide the CD11c^{bright}CD8 α ⁻CD11b⁺ DCs. Very recently an alternative classification of DC subsets has been used, based on the expression of chemokine receptor CX3CR1 and CD103, further confirming the unresolved issue of DC subsets in the mouse.

Plasmacytoid DCs are a specialised DC subset of distinct lineage from CD11c^{high} DCs, and they produce type I IFNs in response to microbial infections. Immature pDCs are poor stimulators of naïve T cell activation, a consequence of their low expression levels of co-stimulatory molecules and intermediate MHC class II expression (Martin et al. 2002), (Asselin-Paturel et al. 2001). As applies to conventional CD11c^{high} DCs, the maturation status of the pDC determines its stimulatory potential, and upon maturation, pDCs acquire the ability to prime T cell responses, albeit less than CD11c^{high} DCs (Salio et al. 2004). Although pDCs have a key role in a

number of immune-mediated diseases such as psoriasis and immunity to tumours and pathogens, pDCs have also the ability to down-regulate the immune response (Abe et al. 2005; Moseman et al. 2004; Ochando et al. 2006). Aspects of pDC migration and function are discussed in this book.

In humans there are two major DC subtypes described, classically defined as Myeloid and Lymphoid. Myeloid DCs are divided into steady state DCs, including Langerhans cells and Interstitial DCs that continually sample the microenvironment, and inflammatory DCs that are generated in response to inflammation (Shortman and Naik 2007). The other prominent DC subtype in the human is the type-I IFN producing pDCs, that respond to viral infection (14). DCs can be generated in vitro from CD14⁺CD11c⁺ monocyte with Granulocyte/Macrophage Colony-Stimulating Factor (GM-CSF) and IL-4 (Sallusto and Lanzavecchia 1994). Alternatively it has been shown that the addition of type-I IFN or TGF- β and GM-CSF can result in DCs deficient in the adhesion molecule DC-SIGN that resembles Langerhans cells (Relloso et al. 2002). Human Myeloid DCs can also be directly obtained ex vivo from the blood by using an antibody that recognises the Blood Dendritic Cell Antigen-2 (BDCA-2⁺) marker. Plasmacytoid DCs can also be generated ex vivo from BDCA-4⁺ precursor and cultured in the presence of IL-3 (Ito et al. 2007).

Altogether the overview of the DC subsets presented here further highlights the complexity of the DC system and raises important questions about the use of DCs in immunotherapy. The growing importance of DCs in the immune system is confirmed by the ever increasing number of published data found in the literature. We felt it timely to commission a contemporary review of the current understanding of DC function in health and disease and their potential manipulation for immunotherapy.

In the first part of this volume, the authors present a very comprehensive review of DCs as pivotal components of the immune system, as already mentioned. In the three initial chapters we will learn what is currently known about activation, migration, and function of DCs as antigen presenting cells and T-cell activators. These chapters lay the foundation for the second part of this volume, which describes the role of DCs in diseases. It is clear that DCs are important in many pathological conditions. However, it would have been very difficult to discuss all of them in one single volume. We have chosen some conditions where significant research has been done in the last few years and where DCs have been shown to be a potential therapeutic target (Rheumatoid Arthritis, Allergic Diseases and Drug Induced Adverse Reaction).

In the last part of the volume we take a closer look at the current status of the specific use of DCs as therapy. The first chapter discusses the intrinsic properties of a subpopulation of pDCs that express IDO following inflammatory conditions and their critical role as regulator of the immune response. The chapter finishes by reviewing the opportunity to manipulate IDO expression in DCs for immunotherapy. This review is followed by four chapters where the authors discuss the manipulation of DCs to induce tolerance in transplantation and autoimmunity, using various drugs (Aspirin, Rapamycin, Dexamethasone and Vitamin D Receptor Antagonists). The last three chapters review the general knowledge on the use of DCs to booster

the immune responses in the treatment of viral infections, cancer and in particular, leukaemia. The first chapter focuses on the development of HIV vaccines based on recombinant adenoviruses (rAd). This review discusses the different types of rAd vectors and their effect in stimulating the DCs and the other cells of the immune system. This chapter is followed by a review of our knowledge of the role played by type I IFNs in the differentiation and activation of DCs towards the priming and expansion of protective antitumour responses. The chapter finishes by discussing how the type I IFNs could be exploited to develop strategies for an effective cancer immunotherapy. Finally, the last chapter discusses the use of DC vaccination to overcome the “intrinsic tolerant state” of patients with acute myeloid leukaemia. The authors also mention the possibility of using an AML-derived cell line (MUTZ-3), equivalent to CD34⁺DC precursor cells, for vaccination purpose.

Altogether, the genetic or pharmacological manipulations of DCs and their potential use in vaccination have raised expectation and hopes in many areas of research concerning the induction of tolerance in autoimmunity and transplantation and the stimulation of the immune responses in cancer and viral infections such as HIV. A great deal of data derived from animal models of human diseases have been published in the last few years from leading laboratories around the world, suggesting that this type of treatment is a real possibility in the very near future.

We hope that this book will give the reader a better understanding of the biology of DCs and why these cells are such important players in the battle against diseases.

We thank our contributors who, with great professionalism, have shared their knowledge and expertise with us.

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