Immune Regulation

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Understanding Dendritic Cell Biology

Dendritic cells (DCs) are professional antigen presenting cells that play a key role in the immune system. Under steady state conditions immature DCs promote tolerance and induction of regulatory cells. Upon pathogen recognition, DCs undergo maturation and initiate the adaptive immune response by priming T cells. DCs dictate the type of adaptive response towards a particular pathogen by secreting different type of cytokines, maintaining an appropriate inflammatory milieu and recruiting specialized effector cells. Such a complex and coordinated response requires DC subset specialization, which is obtained through lineage as well as functional specificity, controlled by complex transcriptional networks. It is therefore essential to understand the transcriptional regulation of existing subsets through the characterization of their developmental cues, as well as identify the transcriptional signature required for the functional properties of each subset.

Defining lineage commitment

Development of DCs occurs in the bone marrow and requires a complex transcriptional lineage specification (fig. 1), which promotes the progression from an uncommitted self-renewing stem cell progenitor to a mature DC. Several transcription factors have been implicated in the development of DC. Some transcription factors impairing DC development also affect other hematopoietic lineages and multiple DC subsets, while some prevent development of a given DC subset. Collectively, the hierarchical requirement of each of them during DC development is still unclear. We could recently show how hetero-complexes of transcription factors are promoting lineage specification. We aim at defining the networks, which are intrinsically required for the establishment of lineage commitment within dendritic cell subsets. Moreover, the transcriptional identity of each subset, which encodes and ensures functional specificity, allowing for the initiation of the appropriate response to a particular pathogen or immunological insult, has to be characterized. Given the critical role of DCs in bridging the innate and the adaptive immunity there is increasing interest in understanding the transcriptional network underlying their development as well as their functional specialization.

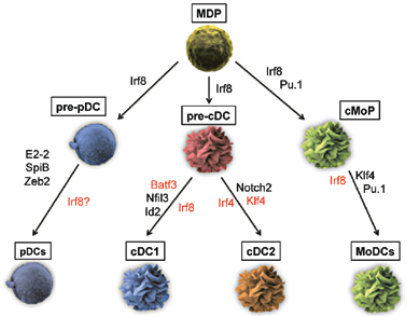

Fig. 1: Dendritic cell development
Dendritic cells develop in the bone marrow from a monocyte-Dendritic cell progenitor (MDP). Lineage commitment is determined by the acquisition of a specific transcriptional landscape at a determined stage of development. Extrinsic factors, proliferation rate and epigenetic changes will influence the expression of given transcription factors and determine the progression into a specific cell lineage, while restricting other fates.

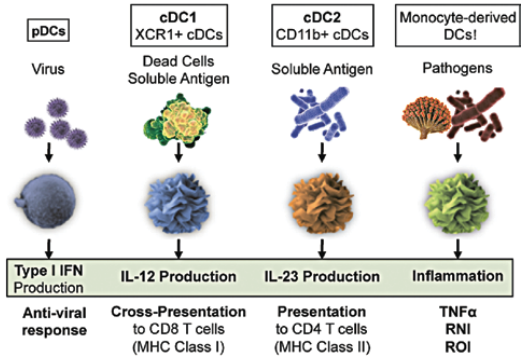

Fig. 2: Dendritic cell subsets
As depicted, we identify four major subsets of DCs. Each subset is able to efficiently recognize and respond to specific pathogens. Following recognition through danger and pattern associated recognition receptors (DAMPs; PAMPs), DC secrete specific cytokines and chemokines leading to the activation of the appropriate innate as well as adaptive immune response.

Deciphering the complexity of cDC2

DCs can be classified in three major branches based on their ontogeny: conventional DC (cDCs), plasmacytoid DCs (pDCs) and monocyte derived DCs. cDCs are further subdivided into cDC1 and cDC2 (fig. 2). cDC1 are a homogenous group, dependent on the transcription factors Irf8 and Batf3, and can be identified across all organs and tissues based on the expression of XCR1. On the contrary, cDC2 are highly heterogeneous, unified only by the expression of Irf4. The complexity of the cDC2 subset was further highlighted by single cell sequencing experiments. Transcriptional profiling of cDC progenitors allowed us to identify Klf4 as a transcription factor involved in the development of a subset of cDC2. A significant reduction of the cDC2 compartment is evident in the absence of the transcription factor Klf4. In some tissues the use of specific markers allowed us to unequivocally identify the Klf4-dependent cDC2 subpopulation, which in skin draining lymph nodes was previously recognized as double negative for the surface markers CD11b and CD24. Despite its identification, the role of this DC subset as well as the functional requirement for Klf4 was unknown. We could show that expression of Klf4 within cDCs is necessary for the induction of Type 2 immunity. Klf4 deficient mice are highly susceptible to parasitic infections, such as the helminthes *Schistosoma mansoni*. Further, impaired Th2 immunity in these mice shows increased resistance to the development of house dust mite induced asthma (fig. 3). The mechanisms underlying the pathogenesis of Th2 immunity are still unclear. The identification of the transcription factor as well as the DC subset involved in Th2 priming will be instrumental to understand how Th2 immunity is established, and potentially lead us to the development of therapeutic interventions.

Selected Publications

Murphy TL, Grajales-Reyes GE, Wu X, Tussiwand R, Briseño CG, Iwata A, Kretzer NM, Durai V, Murphy KM. Transcriptional Control of Dendritic Cell Development. Annu. Rev. Immunol 2016

Everts B, Tussiwand R, Fairfax KF, Huang SC C., Smith AM, O'Neill CM, Lam WY, Edelson BT, Murphy KM, Pearce EJ. CD103+ Dendritic Cells suppress Helminth-driven Type 2 Immunity Through Constitutive Expression of IL-12. J Exp Med 2016

Grajales-Reyes GE, Iwata A, Albring J, Wu X, Tussiwand R, Kc W, Kretzer NM, Briseño CG, Durai V, Bagadia P, Haldar M, Schönheit J, Rosenbauer F, Murphy TL, Murphy KM. Batf3 maintains autoactivation of Irf8 for commitment of a CD8 (+) conventional DC clonogenic progenitor. Nat Immunol. 2015

Tussiwand R, Everts B, Grajales-Reyes G E, Kretzer NM, Iwata A, Bagaitkar J, Wu X, Wong R, Murphy TL, Pearce EJ, Murphy KM. KLF4 expression in conventional dendritic cells is required for T helper 2 responses. Immunity 2015

Tussiwand R and Gautier EL. Transcriptional regulation of mononuclear phagocyte development. Frontiers in Immunology 2015

Murphy TL, Tussiwand R, Murphy KM. Specificity via cooperativity: BATF/IRF interactions control immune regulatory networks. Nat Rev Immunol 2013

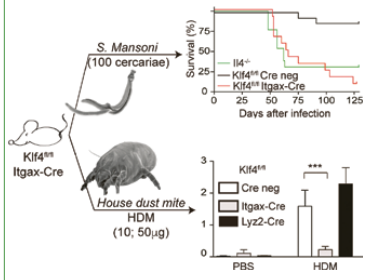

Fig. 3: Dendritic cell subsets
Expression of the transcription factor Klf4 within dendritic cells is required for the induction of Th2 immunity. Klf4 conditional-deficient mice are highly susceptible to *S. mansoni* infection and succumb around 50 days after infection, comparable to IL-4 deficient mice. Also the context of allergic reactions, Klf4 conditional-deficient mice show impaired Th2 immunity. This results in reduced eosinophil recruitment in bronchoalveolar lavage following intra-nasal challenge with house dust mite.