Instruction of effector T cell programs by flexible dendritic cells
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Summary

Adaptive immunity protects against infection and relies on the generation of different effector immune cells, specialized in the clearing of particular types of pathogens. Optimally, type 1 responses are instrumental in the defense against intracellular micro-organisms and type 2 responses are essential in the clearing of helminthic infections. However, aberrant or chronic adaptive immune responses may form a potential threat to host tissues. Negative regulation of adaptive immunity is required to prevent excessive inflammation and is therefore a key element in the prevention of auto-immunity and allergy. Dendritic cells (DC) play a central role in determining the different classes of adaptive immunity, by virtue of the expression of particular sets of polarizing molecules, driving either T helper (Th) 1 cells, Th2 cells or regulatory T cells. The nature of the T cell polarizing capacity of DC is dictated by microbial or tissue-specific information encountered in the peripheral tissues.

In general, the studies in this thesis focus on the modulation of either established effector T cells, in particular Th2 cells dominating in allergic diseases, or on the modulation of naive precursors that may precede the development of allergic diseases in young children.

In the studies of the modulation of existing effector Th2 cell responses, special attention was attributed to the role of the strong Th1-polarizing factor IL-12 and the T cell responsiveness to this factor. In the second part of the studies, the influence of microbial priming on the naive Th cell-polarizing capacity of dendritic cells was investigated in the context of the hygiene hypothesis.

In chapter 2 the stability of the phenotype of fully polarized Th2 cells and their susceptibility to the Th1-driving cytokine IL-12 were investigated. Although Th2 cells are initially unresponsive to IL-12 as a result of the lack of the signaling β2 chain of the IL-12R, restimulation of these cells in the presence of IL-12 resulted in stably reverted Th1/Th0 cells with fully restored IL-12Rβ2 expression and IL-12-responsiveness. Crucial in this respect is that human IL-12Rβ2 expression is transient and subject to regulation upon each restimulation. Consequently, IL-12-unresponsiveness can only be maintained in the continuous absence of IL-12 and presence of IL-4. Therefore, the data suggest that local IL-12 levels rather than the initial phenotype are ultimately decisive for the stability of the polarized Th2 phenotype. It is unlikely that a situation with elevated levels of IL-12 may occur in a fully type 2 polarized cytokine milieu in the lymphoid tissues of allergic patients, but the data suggest that IL-12-promoting therapy may be beneficial in the treatment of allergic diseases. Chapter 3 describes the paradoxical finding that IL-4, just like IFNγ, can induce the production of IL-12 in immature DC, although it inhibits the production of the IL-12p40 subunit. This finding suggests that induction of IL-12 production in a peripheral type 2 cytokine milieu may still occur, and leads to repolarization of effector Th2 cells in vivo.
Chapter 4 gives an overview of the characteristics of polarized Th2 cells and the repolarizing capacity of IL-12. Furthermore, IL-12-promoting therapies to target (ongoing) allergic diseases are discussed.

In view of the above findings and in the context of the hygiene hypothesis, alternative mechanisms were explored that can drive Th1 responses in the absence of IL-12, as newborns, with or without a high risk to develop allergic diseases, still have an undeveloped IL-12-producing capacity and may need such alternative mechanisms to drive early Th1 responses. Chapter 5 describes the development of Th1 cells by the ligation of LFA-1 on naive Th cells by ICAM-1 on DC, which was demonstrated in a model for virus-infected DC. This mechanism was overruled by polarizing cytokines and only played a role in the absence of IL-12 and IL-4. As such it may operate under low cytokine conditions in newborns. The hygiene hypothesis assumes that the exponential rise in childhood allergy is due to a decreased or changed microbial exposure early in life. Negative associations in this respect have been described for e.g. the intestinal microflora. DC are the major cell types to determine the outcome of Th cell polarization and their Th cell polarizing capacity is influenced by microbial priming. Therefore, the study described in chapter 6 investigated the priming effects of gut flora bacteria, both including Gram-negative and Gram-positive species, on the Th cell polarizing capacity of DC. Gram-negative bacteria appeared to prime monocyte-derived DC (moDC) for an enhanced Th1 polarizing capacity, whereas Gram-positive bacteria did not seem to change the Th cell polarizing capacity of DC, at least not in terms of Th1 or Th2 development. Elevated mRNA levels of IL-23 and IL-27, but not IL-12, observed in Gram-negative bacteria-treated DC suggested a putative role in Th1 development for these novel IL-12 family members. However, the concept of a desired Th1 development to counter-balance neonatal Th2 cell responses is gradually overtaken by the idea that regulatory T cells, instead, may counter regulate neonatal Th2 cell responses. In support of this novel view, the hygiene hypothesis is now explained by insufficient negative regulation of hyper-inflammatory processes (e.g. allergic responses) due to a decreased microbial exposure. In addition, certain Gram-positive gut flora bacteria, so called probiotics, rather than Gram-negative gut flora bacteria, have been reported to reduce either the onset or the severity of the symptoms of allergic diseases. These findings cannot be explained by an increased drive for Th1 responses.

In search for novel microbial candidate adjuvants that induce negative regulation and therefore may be useful in the treatment of allergic or auto-immune diseases, several compounds were investigated in chapter 7 for their capacity to prime DC for the instruction of regulatory T cell development. Cordycepin (a 3'-deoxyadenosine derived from the fungus *Cordyceps*) and cholera toxin B (a toxin subunit produced by the bacterium *Vibrio cholerae*) both primed mature moDC to drive the development of regulatory T cells, in part mediated by DC-derived IL-10 (cordycepin) or by a yet unknown membrane-bound molecule (cholera toxin B). Furthermore, Chapter 8 demonstrates that the probiotic bacteria *Lactobacillus reuteri* and *Lactobacillus casei*, but not *Lactobacillus plantarum*, primed moDC for the
development of regulatory T cells via binding of the C-type lectin DC-specific ICAM-3 grabbing non-integrin (DC-SIGN). This is in line with the hygiene hypothesis stating that certain micro-organisms, in particular probiotic bacteria, may induce negative regulation, and may reduce susceptibility to develop allergic diseases. Chapter 9 merges the findings of the last chapters and recent literature data into the concept that exposure to microbial and tissue-specific signals can prime for the generation of either immature or mature regulatory DC subsets that can drive the development of regulatory T cells. These DC subsets appear to exploit unique mechanisms to drive regulatory T cells. It remains to be established whether they have distinct functions, apart from their overlapping roles in protective immunity.