Modulation of human dendritic cell function by therapeutic agents
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Citation for published version (APA):
Summary

Efficient clearance of a certain type of pathogen depends on the induction of the appropriate class of antigen-specific immunity, which can be mediated by type 1 and type 2 CD4+ Th cells (Th1 and Th2 cells), each with distinct functions relating to their unique cytokine profiles. Th1 cells mainly produce IFN-γ, which promotes cell-mediated immunity against intracellular pathogens, whereas Th2 cells predominantly produce IL-4, IL-5, and IL-13, which are critical for IgE-mediated responses against helminths and other extracellular pathogens. Since it is not well understood how protective immunity is established against different types of pathogens and what factors determine the onset of (autoimmune) disease, great efforts have been made to unravel the signals involved in naïve Th cell activation and polarization towards Th1- and/or Th2-type cytokine producing effector cells. DC are highly specialized APC linking innate and adaptive immunity. Data are emerging that DC play a central role in the induction and regulation of Th cell responses. Therefore, it is important to investigate the factors that influence the immunoregulatory function of DC.

In the first part of this thesis a few basic aspects of DC were investigated, such as the antigen-specific T cell stimulatory capacity of DC and their ability to bind and take up mucosal IgA. Subsequent studies, described in the second part of this thesis, were focussed on how therapeutic agents, such as PDE4 inhibitors, type I IFN, and GA, modulate the cytokine production and T cell polarizing capacity of DC.

In Chapter 2 we addressed the question whether priming of monocytes with GM-CSF alone, or in combination with IL-4, would affect their APC function, since these cytokines have been described to promote the development of DC with strong stimulatory potential. We found that priming of freshly isolated monocytes with antigen in the presence of GM-CSF, or GM-CSF and IL-4, strongly inhibited the specific stimulation of the T cells, as compared to monocytes pulsed in the absence of cytokines. This suppression was partially due to the secretion of PGE2 and IL-10 by GM-CSF-exposed monocytes, since the combined use of indomethacin and anti-IL-10 antibodies during GM-CSF incubation and antigen pulsing partially restored T cell growth. As confirmed by culture supernatant transfer experiments, maximal inhibition of T cell stimulation was also dependent on the direct contact between the T cells and GM-CSF-exposed monocytes during antigen-presentation. This implies that GM-CSF may affect the T cell stimulatory potential of monocytes via the induction of soluble as well as membrane-bound inhibitory factors, which is in sharp contrast to its effects on DC function.

In Chapter 3 we investigated how the expression of the FcαRI (CD89) is regulated during DC development and studied whether and how DC interact with mucosal IgA. We show that the levels of FcαRI are strongly decreased upon differentiation from monocyte to DC. We found only minimal binding of serum IgA to monocyte-derived DC but strong binding of secretory IgA (SIgA). The SIgA binding to DC could not be blocked by anti-CD89 blocking antibodies. DC efficiently internalized SIgA, but not serum IgA, and uptake of SIgA could be blocked by specific sugars or partially by Ab reactive with mannose receptor (MR). Importantly, binding and uptake of SIgA was
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not accompanied by signs of DC maturation, such as increased expression of CD86 and CD83 or induction of cytokine secretion. This indicates that at mucosal surfaces DC may interact with mucosal IgA via a C-type lectin receptor-dependent pathway and that this may be a mechanism to modulate the immune response.

In Chapter 4 we first investigated the PDE profile of monocyte-derived DC and found predominant enzymatic activity of PDE4. Subsequently, the modulatory effect of PDE4-specific inhibitors on DC functions such as cytokine secretion and T cell stimulatory and polarizing capacity was investigated. We show that PDE4 inhibitors directly reduce IL-12 and TNF-α secretion by immature DC in response to LPS and CD40L-dependent activation, whereas PDE4 inhibitors did not directly affect cytokine production by CD40L-activated mature DC. Induction of DC maturation in the presence of PDE4 inhibitors did not influence their T cell stimulatory capacity or acquisition of a mature phenotype. However, the ability of PDE4 inhibitor-matured DC to produce IL-12p70 and TNF-α is impaired and consequently they show a reduced capacity to initiate the development of IFN-γ producing (Th1) cells. This indicates that, in addition to their direct inhibitory effect on T cells, PDE4 inhibitors may also reduce inflammatory Th1 responses via modulation of DC.

In Chapter 5 the effects of type I IFN on DC at different stages of maturation were studied. Here we show that type I IFN directly increase the IL-12 production by immature DC but inhibit the IL-12 production by mature DC in response to CD40L-dependent activation. The presence of type I IFN during DC maturation does not affect the IL-12-producing capacity of these cells upon subsequent CD40L activation. Regardless of the maturation stage of the DC we found that type I IFN strongly counteracted the IL-12-enhancing effect of IFN-γ. This indicates that type I IFN affect DC-derived IL-12 depending on the maturation stage of the cells and inhibit the positive circuit between IL-12 and IFN-γ, which may be beneficial to reduce inflammatory processes.

In Chapter 6 we studied the modulatory effects of glatiramer acetate (GA) on the T cell regulatory function of DC and addressed the question whether the effect of GA on Th cells is antigen-presenting cell (APC)-dependent. We demonstrate that DC exposed to GA show an impaired capacity to secrete IL-12 and other inflammatory cytokines in response to LPS and CD40L-dependent activation. DC exposed to GA reduce the development of IFN-γ-producing Th1 cells while promoting the induction of IL-4-producing Th2 cells which is accompanied by enhanced levels of IL-10. The anti-inflammatory effect of GA is mediated via DC as GA does not affect the cytokine profiles of naive Th cells activated in an APC-free system. This indicates that the Th polarizing effects described for GA in MS are mediated via DC.

In Chapter 7 we propose that SlgA at mucosal surfaces interacts with DC via C-type lectin receptors and that this may be a mechanism to induce tolerance. Furthermore, we discuss the finding that therapeutic agents are able to suppress IL-12 secretion by DC and thus reduce the induction of inflammatory Th1-type responses. These findings indicate that, next to their nonspecific anti-inflammatory effect on monocytes/macrophages and Th cells, these agents additionally dampen inflammatory responses by acting at the level of DC.