Harnessing dendritic cells to promote immune tolerance: Opportunities for allergen-specific immunotherapy

Bakdash, G.

Citation for published version (APA):
Bakdash, G. (2013). Harnessing dendritic cells to promote immune tolerance: Opportunities for allergen-specific immunotherapy
SUMMARY

Allergen-specific immunotherapy (SIT) is considered to be the sole curative therapeutic approach of mono allergies. However, the widespread use of SIT is hindered by the small but imminent risk of developing anaphylactic reactions. Another major drawback of SIT is the relatively low efficacy reflected by the long treatment duration. The work described in this thesis aims at establishing the foundations for novel efficacious modalities of SIT. Since the development of immune tolerance mediated by regulatory T (Treg) cells is an essential element for successful SIT, this study focused on the use of regulatory adjuvants, compounds that via their effect on antigen-presenting dendritic cells (DCs) promote the development of Treg cells.

Chapter 1 is a general introduction summarizing current knowledge about the role of DCs in shaping adaptive immunity and immune tolerance, allergy and the principle of SIT along with the mechanisms proposed to mediate its effects. Furthermore, the existing knowledge about the immunological impact of the two regulatory adjuvants used in this thesis: vitamin D3 (VitD) and retinoic acid (RA) was thoroughly introduced.

In Chapter 2 we investigate the differential effects of VitD on two distinct skin DC subsets: epidermal Langerhans cells (LCs) and dermal dendritic cells (DDCs). VitD-Conditioning of both DC subsets inhibited their maturation, inflammatory cytokine production and T cell stimulatory capacity. Furthermore, we found that VitD-treatment of these DC subsets promotes immune tolerance by inducing the development of two distinct types of regulatory T (Treg) cells. Whereas VitD-primed LCs induced the development of $CD25^\text{hi}CD127^\text{lo}Foxp3^+$ Treg cells, VitD-primed DDCs gave rise to $Foxp3^-, IL-10^+$-producing Treg cells. Blocking experiments revealed that LC-derived TGF-$\beta$ is a key factor in the induction of $Foxp3^+$ Treg cells, whereas DDC-derived IL-10 is important for the induction of IL-10-producing Treg cells. These findings can be exploited to enhance the quality of SIT, which is usually applied through the cutaneous route.

Chapter 3 addresses the possible effects of calcidiol, the precursor calcitriol (the physiologically active form of VitD), on DCs. Calcidiol not only exerted an inhibitory effect on DC maturation and altered DC cytokine production, but also primed DCs to promote the development of IL-10-producing Treg cells that act as regulatory T cells suppressing the proliferation of bystander cells. Strikingly, in contrast to the population of IL-10-producing Treg cells induced by calcitriol-primed DCs, the IL-10-producing Treg cells induced by calcidiol-primed DCs exhibited sustained IFN-$\gamma$ production in face of their suppressive capacity. Blocking experiments showed that the immunomodulatory features of calcidiol are dependent on its conversion by DCs into calcitriol. The calcidiol-mediated effects may be of particular interest for the treatment of allergic disease, where concurrent suppression and sustained IFN-$\gamma$ production by Treg cells effectively counterbalance the Th2-dominated immune responses.

The study presented in Chapter 4 aims at elucidating the influence of VitD on the human skin DC subsets, i.e. LCs, $CD14^+$ DDCs and $CD1a^+$ DDCs, in their natural environment. This issue was addressed by intradermal (ID) administration of VitD in a human skin explant system that closely resembles physiological conditions. ID injection of VitD selectively enhanced the migration of $CD14^+$ DDCs. Moreover, ID injection of VitD repressed the LPS-induced T
cell stimulatory capacity of migrating DCs. These migrating DCs collectively promoted the development of suppressive T cells that lacked IFN-γ productivity. Those induced T cells were characterized by the expression of Foxp3.

In Chapter 5 we show that targeting of the major allergen of birch pollen, Bet v 1d, to DCs via the DC-specific surface molecule DEC205 effectively activates allergen-specific T cells. Furthermore, the concomitant presence of VitD during Bet v 1d targeting impedes the proliferation of Bet v 1d-specific T cells and modifies their cytokine production. These findings suggest that combined allergen targeting and regulatory adjuvant might be a promising approach to enhance the quality of SIT.

In Chapter 6 we investigate the immunomodulatory properties of RA on human DCs and subsequent development of T cells. RA primes DCs to express CD103 and produce RA themselves. These RA-conditioned human CD103+ RA-DCs did not substantially enhance Foxp3 expression by primed T cells but rather induced gut-homing T cells producing high levels of IL-10, which were functional suppressive Treg cells. IL-10 production was dependent on DC-derived RA and was maintained when DCs were stimulated. In parallel, RA-conditioning of DCs did not affect inflammatory cytokine production by DCs and IFN-γ production by induced T cells thereafter. Furthermore, the mere presence of TGF-β during CD103+ RA-DC-driven T cell priming favored the induction of Foxp3+ Treg cells over IL-10+ Treg cells. Similar results were acquired when naïve CD4+ T cells were stimulated by αCD3 and αCD28 antibodies, instead of DCs, in the presence of RA. These findings not only introduces a novel role of RA in maintaining intestinal tolerance, but also poses RA as an effective immunomodulatory adjuvant that can be applied for the treatment of chronic inflammatory diseases, like autoimmune and allergic disorders.

In Chapter 7 our findings in this thesis are discussed in relation to the current knowledge in relevant fields. We also address how these findings can be integrated into clinically applied SIT protocols, and the obstacles limiting the application of the novel approaches introduced in this thesis.