The role of dendritic cells in adjuvant-induced immune responses

Akademisk avhandling

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Avhandlingen baseras på följande arbeten:

I. **The subcellular location of antigen expressed by adenoviral vectors modifies adaptive immunity but not dependency on cross-presenting dendritic cells**
Henning P*, Gustafsson T*, Flach C-F, Hua Y-J, Strömbeck A, Holmgren J, Lindholm L, Yrlid U.
Eur. J. Immunol. 2011, 41: 2185-2196.

II. **Direct interaction between cholera toxin and dendritic cells is required for oral adjuvant activity**
Gustafsson T, Hua Y-J, Dahlgren M, Livingston M, Johansson-Lindbom B, Yrlid U.
Submitted manuscript

III. **T follicular helper cell development and germinal center formation in the absence of conventional dendritic cells**
Gustafsson T*, Dahlgren M*, Livingston M, Cucak H, Johansson-Lindbom B#, Yrlid U#.
In manuscript

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The role of dendritic cells in adjuvant-induced immune responses

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Dendritic cells (DCs) are sentinels of mucosal surfaces, residing directly under the epithelial layer. DCs are among the first cells that come in contact with pathogens and have the unique ability to activate T cells that subsequently can aid B cells to produce antibodies with high affinity. T and B cells constitute our immunological memory that protects us from reinfections – the basis for vaccination. Vaccines composed of purified antigens, confer high specificity but have low intrinsic immunogenicity, and require therefore an adjuvant that enhances the response. The most potent adjuvants are often toxic, and consequently a limited number of adjuvants are available for clinical use, mucosal adjuvants in particular. Therefore, a better understanding is needed concerning the interactions between adjuvants and DCs in order to unveil the mechanisms of adjuvanticity. Here we have *in vivo* studied the role of DCs and the characteristics of the immune response after immunization with different adjuvants.

Adenoviral (Ad) vaccine vectors inducing expression of ovalbumin (OVA) at different subcellular locations were used in a mouse model in which conventional DCs (cDCs) could be depleted. We show that cDCs are required for activation of T cells although a direct transduction of cDCs by Ad-vectors is not essential. Further we determine that secreted and membrane-anchored antigens are superior at activating antigen-specific $CD4^+$, cytotoxic $CD8^+$ T lymphocytes as well as generating a serum IgG response compared to intracellulary expressed OVA.

Cholera toxin (CT) is one of the most potent mucosal adjuvants. CT binds the ubiquitously expressed ganglioside GM1 leading to efficient uptake that in epithelial cells results in secretion of fluid into the lumen. After oral immunization with OVA and CT we find that chimeric mice lacking GM1 on hematopoietic cells, and specifically GM1-expressing DCs, fail to induce adaptive immune responses to OVA. We conclude that CT does not require the toxic epithelial cell interaction for its adjuvant activity but is dependent on direct binding of GM1 on intestinal DCs.

To become plasma cells producing high affinity antibodies, B cells must undergo affinity maturation in the germinal center where they are dependent on the help of follicular helper T cells. In DC-depleted mice, we show that immunization with the adjuvant poly(I:C) and non-limiting doses of OVA generates follicular T helper cells (Tfh) and germinal centers in absence of DCs. In contrast, B cell interactions are required for a fully differentiated Tfh phenotype and the activation of a Th1 mediated T cell response is totally dependent on DCs.

Strategies targeting vaccine antigens to DCs are becoming more promising as novel DC-specific receptors are being discovered. Taken together our results show great heterogeneity concerning the role of DCs in adjuvant-induced immune responses. How to modulate and take advantage of the interactions between adjuvants and DCs will be crucial knowledge in the construction of future more effective and safe vaccines.

Keywords: Dendritic cells, adjuvant, mucosa, adenovirus vector, cholera toxin, T follicular helper cells

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