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Identification of Target Structures for New Vaccines Specifically Directed at Dendritic Cells

Author: Lotte Hatting Pugholm,Laboratory of Immunology, Department of Health Science and Technology, Aalborg University, Aalborg, Denmark

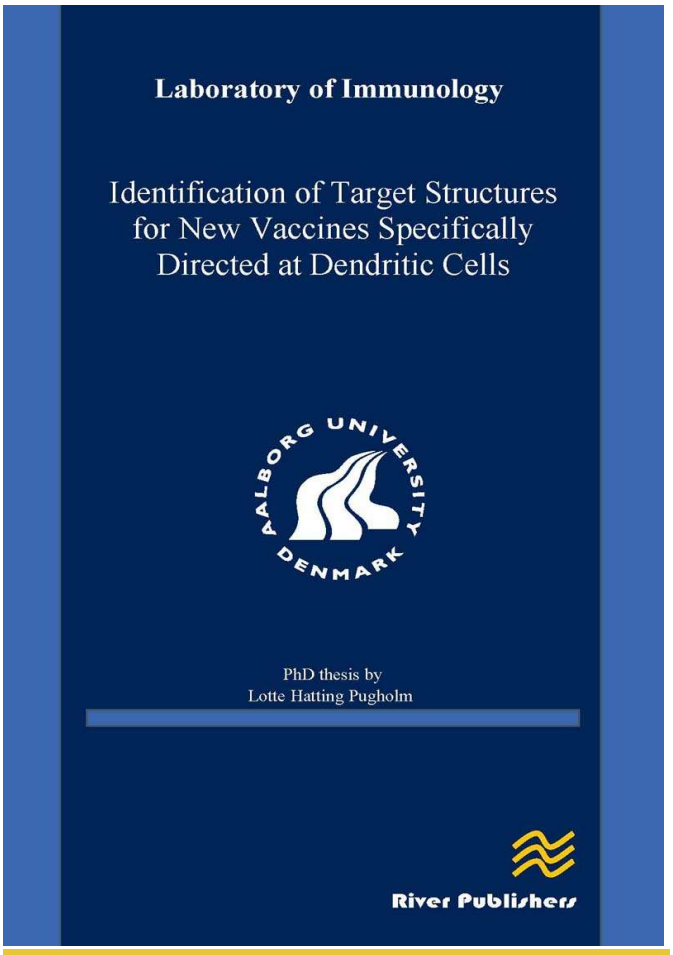
Dendritic cells (DCs) are superior antigen presenting cells (APCs) that are important for the initiation adaptive of immune responses. They are uniquely equipped for the activation and expansion of both naïve and memory T cells. In fact, studies have shown that direct delivery of antigens (Ags) to DCs may augment both T cell responses and humoral immunity. For this purpose, DCs express a unique pattern of cell surface receptors that can be employed as target structures for such targeted delivery of Ags to DCs. Different surface receptors on DCs will, to a varying extent, lead to internalization, processing and presentation of the Ag to T cells. Depending on the intracellular routing of the Ag, antigenic peptides are presented on MHC class I and/ or class II facilitating induction of different T cell responses. A number of different target receptors have been assayed for this purpose, but several other DC surface molecules deserve examination for their usefulness for Agdelivery. Antibodies against several of these surface receptors have become commercially available, and these monoclonal antibodies (mAbs) can be used as vehicles to deliver Ag to DCs. The present thesis employs a strategy in which monoclonal rat antibodies against surface receptors on murine DCs act as both targeting devices (the Ag-binding parts of the molecule) and as Ag (epitopes on the rat immunoglobulin that are immunogenic in the mouse). A panel of such rat anti-mouse mAb directed against different receptors on DCs was employed in this thesis. Ten potential target receptors were selected – CD11c, CD36, CD205, CD206, CD209, Clec6A, Clec7A, Clec9A, Siglec H and PDC-TREM - and each receptor was investigated for its ability to lead to Ag presentation and thereby T cell activation.

In the first part of this thesis, targeted delivery of Ag to ten different target receptors was studied in vitro on murine spleen cell cultures using Ag-induced cytokine production from T cells as readout. The assay developed for this purpose allowed simultaneous screening of a large number of potential target receptors and facilitated direct comparison between the different targets regarding strength and character of the T cell responses induced by the targeted DCs. We found that targeting of Ag to CD11c, CD36, CD205 and Clec7A led to positive IFN-? responses compared to the non-targeted isotype control. Regarding induction of IL-4, CD36 and CD205 did also produce positive IL-4 responses, while no positive responses were obtained by the non-targeted isotype control.

In the second part of this thesis, Ag-delivery to DCs was performed in vivo. Mice were immunized with monoclonal target antibodies specific for the ten receptors, and functional presentation of antigenic peptides by DCs were measured as the ability to induce humoral and cellular responses in the mice.

The results demonstrated that Ag-delivery to different targets on DCs in vivo elicited humoral responses of varying strength and IgG subclass composition. Targeting Ag to CD11c, CD36, CD205, PDC-TREM, Clec6A and Clec7A induced very strong antibody responses compared to the non-targeted control. In contrast, Ag-delivery to CD206, CD209, Clec9A and Siglec H showed responses comparable to those elicited by the nontargeted controls. The IgG subclass composition of the antibody responses induced by Agdelivery to the different receptors was also determined. All responses were dominated by IgG1, but high IgG1 levels were obtained by CD11c, CD36 and CD205. In contrast, Agdelivery to Clec7A induced robust amounts of IgG2a indicating the presence of a manifest Th1 component in the immune responses of these mice.

To the best of our knowledge, PDC-TREM has not previously been investigated as a target receptor for Ag-delivery to DCs. The results obtained in this study indicate that PDCTREM, besides being involved in the production of type I IFNs by pDCs, may function as an endocytic receptor mediating Ag presentation for T cells. As such, PDC-TREM might be a potential target for future DC-directed vaccines.



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