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Novel insights in MHC class II antigen presentation

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Citation

Hoorn, B. M. van den. (2011, April 6). *Novel insights in MHC class II antigen presentation*. Retrieved from <https://hdl.handle.net/1887/16694>

Version: Corrected Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).

Novel Insights in MHC Class II Antigen Presentation

Tineke van den Hoorn

Novel Insights in MHC Class II Antigen Presentation

proefschrift
ter verkrijging van
de graad van Doctor aan de Universiteit van Leiden,
op gezag van Rector Magnificus Prof. mr. P.F. van der Heijden,
volgens besluit van het College voor Promoties
te verdedigen op 6 April 2011
klokke 15:00 uur

door

Berendina Maria van den Hoorn

Geboren te Nunspeet
In 1981

Promotiecommissie

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Cover: Downregulation of Vps28 in MelJuSo cells leads to enlarged MHC class II containing vesicles presented in artificial colours

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The research described in this thesis was performed at the Division of Cell Biology II of the Netherlands Cancer Institute (NKI/ AvL) and supported by The Netherlands Organization for Scientific Research (NWO) and the Dutch Cancer Society (KWF)

Financial support for the publication of this thesis was provided by: the Netherlands Cancer Institute (NKI / AvL) and the Dutch Society for Microscopy.

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Scope of the thesis

Major Histocompatibility Complex class II (MHC-II) molecules present antigens to CD4⁺ T-cells, thereby initiating adaptive immune responses against infections. MHC-II is also involved in the control of cytotoxic T-cell activation, maintenance of self-tolerance and autoimmune responses. A better understanding of the regulation of this master regulator of immune responses is needed to develop new drug, antibody or peptide-based therapies to improve immune responses against infection and cancer or to reduce these in case of autoimmunity.

A general introduction into the MHC-II antigen presentation pathway is given in **Chapter 1**. In this review, the classical picture of MHC-II antigen presentation has been decorated with novel findings from recent literature. This includes also some of the latest attempts to manipulate MHC-II antigen presentation by compounds, antibodies and/or peptides.

An important part of MHC-II antigen presentation process is the loading process that occurs on subdomains in the MHC-II compartment (MIIC), which has a multivesicular structure. On the intraluminal vesicles (ILV) of the MIIC, MHC-II interacts very efficient with its chaperone HLA-DM (DM). In **Chapter 2** we investigated whether tetraspanin proteins, known for their tendency to be organized in protein microdomains, could function as a scaffold for protein interactions, hence facilitating the interaction between MHC-II and DM. Using sensitized emission Fluorescence Resonance Energy Transfer (seFRET) we visualized the efficiency of dynamic homo- and hetero-typic interactions between CD63 and CD82. While the two tetraspanins interacted more efficiently with each other on the limiting membrane of MIIC, both MHC-II and DM preferable interacted with CD63 on ILVs. At the limiting membrane MHC-II favoured interactions with CD82, which can be also observed at the plasma membrane. This suggests that the tetraspanin network is dynamic in MIIC reorganizing the MHC-II and DM molecules thus affecting immune function.

Although the MHC-II antigen presentation pathway is studied in detail, we still aimed at a better understanding of this process using an unbiased screen. In **Chapter 3** and **4** we describe our genome-wide approach combined with systems biology, which we designed to define new players and reveal their complex relationship with known factors. Combining information on the influence of the new players identified on different steps in the MHC-II pathway disclosed hidden relationships. This was followed by in-depth investigation on novel factors controlling MHC-II cell surface expression in immature Dendritic Cells. One of these novel factors, the undescribed GTPase Arl14/ARF7, was studied in further detail. Using information from our databases and applying tools to define novel interactions revealed a function for Arl14/ARF7 in actin-based transport of MHC-II containing vesicles, which included PI3K, PIP5K, ARF7EP and the actin motor MYO1E. In these chapters, we show how a genome-wide study can be translated into 'new biology'.

Finally, **Chapter 5** summarizes the results from these studies and places them into perspective followed by an outlook on the possible implications and applications of these new findings.

