Role of the chaperone gp96 for intestinal innate immunity, ER stress and the induction of tolerance

Summary / Zusammenfassung
We have studied the role of the chaperone gp96 for intestinal innate immunity and the induction of tolerance since 2½ years in our ongoing SNF project. Gp96 protein is a heat shock protein normally located in the endoplasmatic reticulum (ER). It binds peptides (antigens) and can be secreted. Following re-internalization of the gp96-peptide-complex by antigen presenting cells (APCs) the antigens can be transferred to MHC molecules mediating immune reactions or tolerance depending on the local concentration of gp96. Whereas it has been suggested that gp96 may be the major chaperone for Toll-like receptors (TLRs) our recent data from the first funding period demonstrate that this is likely not the case. However, we and others found that gp96 is involved in ER stress reactions that contribute to chronic inflammation in diseases such as inflammatory bowel diseases (IBD).

Intestinal macrophages (IMACs) represent one of the largest macrophage populations of the human body. They constitute a tolerogenic cell type without expression of “typical” macrophage activation receptors. IMACs are of crucial importance for pathogen recognition at the mucosal surface and an impairment of their innate immune functions is associated with the pathogenesis of IBD in particular Crohn’s disease (CD). Studying this cell population since 1995 we found gp96 to be specifically induced during the differentiation of IMACs which could be confirmed in detailed studies during the last years. Gp96 is a chaperone which was reported to be essential for toll like receptor function. We demonstrated that gp96 treatment ameliorates intestinal inflammation in mice and generated cell specific conditional knock out mice for macrophages and epithelial cells to further study this function. Gp96 is also a target and regulator of ER stress as we could recently demonstrate. As ER stress is supposed to play a role in IBD pathogenesis it will be important to elucidate the exact function of gp96 during ER stress reactions in IBD mucosa.

Based on our recent findings we aim to further analyze 1) in which cells gp96 is essential for the maintenance of tolerance against commensal bacteria (“function in normal mucosa”) and 2) why the loss of gp96 protein in IMACs during CD contributes to the loss of tolerance (“contribution to CD pathogenesis”).

Specific aims
A. Clarification of the uptake mechanisms for gp96 in iMACs and ivDCs.
B. Impact of ER stress on gp96 function and vice versa in vitro and in vivo.
C. T-cell response upon peptide presentation via gp96 and IMACs in vitro and in vivo.
D. Role of gp96 expression in IEC and iMACs for colitis, intestinal barrier function and commensal flora in vivo.

The long term goal will be a better understanding of mucosal tolerance and the development of new treatment options for chronic mucosal inflammatory diseases such as CD.

Weitere Informationen unter http://p3.snf.ch/project-138410

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