Celiac disease : how complicated can it get?

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The Nederlandse Coeliakie Vereniging supports scientific research. Also, the NCV organizes contact amongst fellow-sufferers, offers and spreads information, informs and is active in advocacy for persons with coelic disease or dermatitis herpetiformis (www.glutenvrij.nl).

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SCOPE OF THIS THESIS

Scope of this Thesis

Celiac disease (CD) is a common inflammatory disorder of the small intestine, which is triggered by ingested gluten proteins. Previous studies identified crucial steps in the development of celiac disease and based on this knowledge, we propose a threshold model for the development of celiac disease, which is described in chapter 1. It has also become clear that adult-onset celiac disease has a higher frequency of developing complications: refractory celiac disease (RCD) and enteropathy associated T cell lymphoma (EATL). About a decade ago, RCD was subdivided into RCD type I and RCD type II. This division was based on the respective absence or presence of an aberrant intraepithelial lymphocyte (IEL) population. These aberrant IELs were defined as surface TCR-$CD3^-CD4^-CD8^-CD7^+CD103^+$, intracellular $CD3^+$ cells and were identified as the missing link between regular IELs in uncomplicated celiac disease and lymphoma cells in EATL. The function and cellular origin of the aberrant IELs, however, remained unclear. The aim of this thesis was, therefore, to gain more insight in the phenotypical and functional characteristics of aberrant IELs as this might help to understand the events leading from uncomplicated CD to RCD II and gastrointestinal lymphoma.

Chapter 1 provides an overview of the pathogenesis of uncomplicated CD, including the involvement of the disease predisposing HLA-DQ2 and HLA-DQ8 molecules and their role in the presentation of gluten derived peptides. Based on the available data we propose a threshold model in which the efficiency of gluten presentation to $CD4^+$ T cells determines the likelihood of developing CD and its complications.

Until recently, aberrant IELs were mainly investigated in situ due to lack of model systems. This limited the type and extent of experiments to investigate molecular events linked to the development of RCD II and EATL. In *chapter 2* we describe the isolation and propagation of three cell lines from duodenal biopsies of three individual RCD II patients that display a surface TCR-$CD3^-CD4^-CD8^-CD7^+CD103^+$, intracellular $CD3^+$ phenotype that is characteristic for the aberrant cells found in patients with RCD II. We used these cell lines as a model for aberrant IELs in all the studies described in this thesis. In *chapter 2* we studied the presence and functionality of the individual TCR and CD3 chains.

In active celiac disease, regular TCR^+ IELs acquire an NK cell receptor repertoire through which they can lyse epithelial cells. Much less is known about the contribution of aberrant IELs to tissue damage in RCD II and EATL. In *chapter 3* we used the RCD cell lines to investigate the specificity of cytotoxicity of aberrant IELs and the receptors involved.

In *chapter 4* we studied the ability of the RCD cell lines to secrete cytokines after triggering with an array of stimuli. This chapter also suggests a novel role for the activation marker CD30 on (pre)malignant IELs in RCD II and EATL.

The exact cellular origin of aberrant IELs is still unclear. From *chapter 2* we learned that intracellular, all CD3 chains were present, whereas the TCR chains were not always present. Furthermore, the CD3 complex was functional as introduction of exogenous TCR chains resulted in surface TCR-CD3 expression. In *chapter 5* we performed genomic,

transcriptomic and flowcytrometric analysis of the RCD cell lines as a further step to determine the cellular origin of aberrant IELs. We demonstrate that cells with an “aberrant” phenotype are present in the intestinal epithelium of healthy individuals as well. This led us to propose that such cells are part of the normal lymphocyte repertoire and most likely the precursors of the monoclonal aberrant cell populations found in patients with RCD II and EATL. Moreover, these data indicate that aberrant IELs are not derived from mature T cells.

In *chapter 6* the relevance of this thesis and directions for further research and future therapeutic possibilities are discussed.