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Interventional studies on immunological balance in IBD and allergic asthma

AKADEMISK AVHANDLING
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ABSTRACT

We have studied a role of immunological balance in connection to allergen challenge in asthma patients and in connection to apheresis treatment in inflammatory bowel disease (IBD) patients.

It has been suggested that T-helper type 2 cells become recruited into the bronchial mucosa and regulate allergic asthma reaction. Patients who mounted a late-phase reaction in connection to allergen challenge were designated dual responders opposite to single responders. Our finding that IL4+CD4+ cells decreased in the patient group and IFN-γ + CD4+ cells decreased in the single responders after allergen challenge suggests the active traffic of both Th1 and Th2 cells into bronchial mucosa. A diminished capacity to down-regulate the Th2 response by recruitment of sufficient number of IFN-γ positive CD4+ lymphocytes was suggested as explanation to the late phase symptoms in the dual responders.

A previously proposed mechanism of granulocyte- and monocyte adsorbing apheresis (GMA) is that in removing activated granulocytes and monocytes the production of pro-inflammatory cytokines, predominantly TNF-α will be reduced. Following GMA in patients with chronic, active IBD, IFN-γ-positive lymphocytes decreased in post-treatment biopsies in responders and appeared to predict the maintenance of long-term remission or response after 12 months.

The finding of down regulation of IFN-γ+CD4+ cells in post-treatment blood samples and IFN-γ+ cells in post-treatment biopsies indicates that the mechanisms of GMA are complex and may influence the Th-balance.

Given that FoxP3+ T regulatory cells and Toll Like Receptor (TLR) expression are key actors in mucosal immunoregulation we extended the previous study to identify the dynamics of these actors in the intestinal mucosa in relation to clinical improvement following GMA. The number of FoxP3+ cells and TLR-2 expression significantly decreased in post-treatment biopsies. The down regulation of FoxP3+ cells and TLR-2 expression mirrored clinical improvement in patients with active IBD after GMA. The results suggest a potential role of these cells in the pathogenesis of IBD and the induction of immunological tolerance in the mucosa.

The effect of apheresis system lines on soluble regulatory molecules (which are important for the immunological balance) has not been studied before, but was assessed on selected regulatory molecules during a safety study on a modified Cellsorba (device for leukacytapheresis (LCAP)). An important observation was that LL-37 increased at all apheresis sessions within the apheresis plastic lines. LL-37 is a major constituent of neutrophil granules. The peptide mediates a wide range of immunomodulatory actions (microbicidal and chemokine for granulocytes, monocytes, mastcells and T lymphocytes, it suppresses TLR-induced secretion of proinflammatory cytokines) and may therefore have a positive impact on the immunological tolerance and which may contribute to LCAP efficacy on UC.

In summary: We have suggested that differences in response to allergen can depend on different capacity to maintain and restore the immunological balance in bronchial mucosa, the Th-balance. Diminished capacity to recruit IFN-γ+ CD4+ lymphocytes is associated with development of an additional so called late-phase reaction. We have demonstrated that one plausible mechanism of GMA are immunomodulating involving down regulation of IFN-γ+ lymphocytes hereby influencing the Th-balance. The clinical improvement in IBD after GMA was associated with improved immunological tolerance mirrored by down regulation of FoxP3+ cells and TLR-2 expression. And finally, we have described generation of LL-37 in the plastic lines of apheresis system, which may also have a positive effect on the immunologic tolerance.

The results emphasize that the restoration of the immunological tolerance can be a key to future successful therapeutic strategy.

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