



Dysregulated Mucosal Immune Responses in Microscopic Colitis Patients

av

Sezin Günaltay

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Opponent: Professor Allan M Mowat
Glasgow Universitet
Glasgow, Storbritannien

Örebro universitet
Institutionen för Hälsovetenskap och Medicin
701 82 ÖREBRO

Abstract

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Microscopic colitis (MC), comprising collagenous colitis (CC) and lymphocytic colitis (LC) is a common cause of chronic watery diarrhea. The diagnosis relies on typical histopathological changes observed upon microscopic examination. The studies in this thesis investigated innate and adaptive immune responses in the colonic mucosa of MC patients, also comparing patients with active disease (CC and LC) and histopathologically in remission (CC/LC-HR). We first analyzed expression of interleukin-1/Toll-like receptor (IL-1/TLR) signaling regulators in MC patients (Paper I). Our results showed enhanced IRAK-M, microRNA-146a, -155 and -21 expressions, whereas IL-37 gene expression was reduced in CC and LC patients as compared to non-inflamed controls. These results suggest different pathophysiological mechanisms in MC patients. The mixed inflammatory cell infiltrations seen in the lamina propria of MC patients might be a result of dysregulated expression of chemotactic mediators. In Paper II, we showed that MC patients display mainly an increased expression of chemokines and chemokine receptors in active disease as compared to non-inflamed controls. In Paper III, we examined if the decreased IL-37 expression seen in Paper I could mediate the upregulation of chemokines seen in Paper II. We showed that a relatively small reduction in the ability of epithelial cells to produce IL-37 results in mainly increased chemokine expressions in a pattern similar to the findings in Paper II. In order to understand the nature of infiltrating T cells commonly observed in MC patients, we analyzed the T cell receptor (TCR) β chains in colonic biopsies of MC patients (Paper IV). Our results showed significant differences in TCR β repertoire, which suggests selectively expanded T cell clones in active MC and histopathologically in remission patients. Altogether, these results i) increase the knowledge of MC pathogenesis by showing changes in TLR signaling regulators, enhanced chemokine and their receptor expressions involved in a mixed immune cell infiltrations and selectively expanded T cell clones in CC and LC patients, as well as in histopathological remission ii) might potentially increase the possibility of more target-specific therapies based on IL-37 induction, chemokines or chemokine receptor inhibitions, or hindering T cell infiltration according to TCR clonality.

Keywords: Microscopic colitis, collagenous colitis, lymphocytic colitis, TLR, chemokine, chemokine receptor, IL-37, TCR.

Sezin Günaltay, Faculty of Medicine and Health
Örebro University, SE-701 82 Örebro, sezin.gunaltay@oru.se