Göteborg, 2023

Macrophages in Crohn´s Disease

Innate immune cellular and molecular mechanisms driving intestinal inflammation and fibrosis

Akademisk avhandling
Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin,
Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson,
Medicinaregatan 3, torsdag den 21 december, klockan 13:00
av **Frida Gorreja**

Fakultetsopponent:
Dr Ola Winqvist, Professor & Överläkare
ABC labs, Sverige

Avhandlingen baseras på följande delarbeten

I. **Gorreja F**, Caër C, Rush S.T.A, Forsskål S.K, Härtlova A, Magnusson M.K, Bexe-Lindskog E, Börjesson L.G, Block M, Wick M.J. MEFV and NLRP3 Inflammasome Expression Is Attributed to Immature Macrophages and Correlates with Serum Inflammatory Proteins in Crohn´s Disease Patients. Inflammation. 2022;45(4):1631-1650. doi:10.1007/s10753-022-01647-8.

II. Caër C, **Gorreja F**, Forsskåhl S.K, Brynjolfsson S.F, Szeponik L, Magnusson M.K, Börjesson L.G, Block M, Bexe-Lindskog E, Wick M.J. TREM-1+ Macrophages Define a Pathogenic Cell Subset in the Intestine of Crohn's Disease Patients. Journal of Crohn´s and Colitis. 2021 Aug 2;15(8):1346-1361. doi:10.1093/ecco-jcc/jjab022.

III. **Gorreja F**, Bendix M, Rush S.T.A, Maasfeh L, Savolainen O, Dige A, Agnholt J, Öhman L, Magnusson M.K. Crohn´s Disease derived fecal supernatants induce altered polarization of M2 macrophages and intestinal fibroblasts. 2023 (*Submitted manuscript*).

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Innate immune cellular and molecular mechanisms driving intestinal inflammation and fibrosis

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Abstract

Macrophages and their interactions with the lamina propria and luminal microenvironment are crucial in the pathogenesis of Crohn´s disease (CD), a chronic inflammatory disease with a strong inflammatory innate immune involvement. Therefore, interpreting macrophage activity in the intestinal microenvironment may identify treatment targets beneficial for at least a subgroup of patients. The overall aim of this thesis was to establish innate immune cellular and molecular mechanisms driving intestinal inflammation and fibrosis in CD. In more detail, it was aimed to determine the inflammasome components and TREM-1 receptor expression in CD in relationship to macrophage phenotypes, as well as to evaluate the effects of the CD fecal microenvironment on macrophages and fibroblasts phenotypes. The first paper showed that inflammasome component expression in CD was location- and cell-specific, and MEFV and NLRP3 inflammasome expression in ileal CD was attributed to the accumulation of immature macrophages. The second paper demonstrated that TREM-1 expression was higher in CD and attributed to increased numbers of immature macrophages increase in CD, defined as $CD14^{+}CD11c^{+}HLA\text{-}DR^{int/high}$, as well as lamina propria microenvironment changes in CD. The third paper established that the CD fecal microenvironment polarize the *in vitro* tissue-resident macrophages into a more pronounced anti-inflammatory phenotype while induce pro-inflammatory but no fibrosis-related changes on intestinal fibroblasts.

Overall, this thesis concludes that the increase of inflammasome and TREM-1 expression on macrophages, and the influence of fecal microenvironment on macrophages might be potential targets for treating CD. Forthcoming studies should aim to provide functional understanding and identify therapeutic targets in larger patient cohorts to meet the needs for improved treatments.

Keywords: macrophages, inflammatory macrophages, tissue-resident macrophages, efferocytosis, innate immunity, myeloid cells, fibroblasts, fibrosis, inflammasomes, Crohn´s disease, inflammatory bowel diseases, digestive diseases, intestinal immunity, mucosa, immunology, intestinal inflammation, serum systemic inflammation, microbiota, metabolites

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