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GM-CSF AUTOANTIBODIES: PREDICTORS OF CROHN'S DISEASE DEVELOPMENT AND A NOVEL THERAPEUTIC APPROACH

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Background: Crohn's disease (CD) is a heterogenous, chronic inflammatory disorder driven by a combination of genetic, environmental, and microbiota-dependent risk factors. Mononuclear phagocytes (MNP) are crucial cells that maintain intestinal homeostasis. An important cytokine for MNP survival and function is granulocyte-macrophage colony stimulating factor (GM-CSF). Interestingly, several studies reported CD-associated genetic risk variants within the GM-CSF receptor and its downstream signaling components. Furthermore, high titers of autoantibodies specific to GM-CSF can be detected in CD patients. Taken together, this data suggests an important role for GM-CSF in abrogation of CD development in a subgroup of patients.
Aims: This study sought to investigate the function of GM-CSF autoantibodies in CD.
Methods: We retrospectively quantified and characterized GM-CSF autoantibodies in sera of 220 CD, 200 ulcerative colitis (UC) patients, and 220 healthy controls (HC) sampled at 3 time points prior to disease diagnosis and one time point after diagnosis. ELISA was used to determine GM-CSF autoantibody titers and isotypes followed by in vitro multiplexed mass cytometry (CyTOF) neutralization assays on peripheral blood mononuclear cells. Flow cytometry and CyTOF were used to map the profile of immune cells isolated from inflamed and non-inflamed CD mucosa.
Results: Our data demonstrates that GM-CSF autoantibodies are specific to CD, significantly elevated up to 7 years prior to diagnosis of disease, and correlate with disease location, severity, and complications at the time of diagnosis. Moreover, in contrast to GM-CSF autoantibodies in pulmonary alveolar proteinosis patients, CD-associated autoantibodies neutralize GM-CSF via specific recognition of post-translational modifications (PTM), affecting MNP function. Removal of PTM enabled GM-CSF to escape autoantibody binding and restored MNP response to GM-CSF in the presence of neutralizing antibodies, indicating a potential therapeutic avenue.

Furthermore, we identified group 3 innate lymphoid cells (ILC3) as a major source of GM-CSF in the healthy intestinal tract, suggesting intriguing crosstalk of MNP and ILC3 across the GM-CSF-GM-CSFR axis.
Conclusions: Our results identify GM-CSF autoantibodies as predictive serological biomarker for CD in a subgroup of patients presenting with severe and complicated form of disease at the time of diagnosis. The presence of GM-CSF autoantibodies precedes the onset of CD by several years and likely abrogates homeostatic immune cell crosstalk involving ILC3 and MNP, suggesting the development of a pre-diseased state in CD patients.

Funding Agencies: CIHRDr. Edward Ketchum Graduate Scholarship