Investigating chemerin/CMKLR1 signalling as a novel link between obesity and inflammatory bowel disease

Helen J. Dranse¹, Jillian L. Rourke¹, Andrew W. Stadnyk²-³, Christopher J. Sinal¹
¹Department of Pharmacology, ²Department of Microbiology and Immunology, ³Department of Pediatrics
Dalhousie University, Halifax, Nova Scotia, Canada

BACKGROUND

- Bioactive chemerin is a potent chemoattractant that recruits cells expressing the G-protein coupled receptor Chemokine-like receptor 1 (CMKLR1) to sites of inflammation.
- Clinical studies demonstrate increased circulating levels of chemerin in several inflammatory bowel diseases (IBD) such as Crohn’s disease and ulcerative colitis; in murine models, chemerin injection has been reported to exacerbate colitis.
- Chemerin is an adipocyte-secreted signaling molecule (adipokine) and circulating levels are correlated with adiposity.
- Increased WAT mass negatively impacts severity and treatment of IBD; however, the link between adiposity and IBD is poorly understood.

Hypothesis: Chemerin plays a pro-inflammatory role in colitis development and loss of chemerin signaling will protect against disease severity.

RESULTS

1. Chemerin and CMKLR1 expression both increase in the cecum and distal colon following DSS treatment.

2. Local chemerin secretion from the colon increases in a proximal-distal gradient following DSS treatment.

3. Circulating levels of relative bioactive chemerin increase throughout DSS treatment.

4. CMKLR1-null mice have a slower onset of disease.

5. CMKLR1-null mice have similar levels of colon inflammation but increased local chemerin secretion.


CONCLUSIONS & FUTURE STUDIES

- Chemerin expression, secretion, and processing increase along a gradient positively associated with the severity of colon inflammation, and circulating bioactive chemerin levels increase following DSS treatment.
- C57BL/6 and C57BL/6-14/16 (not shown) weak-null CMKLR1 KO mice develop signs of clinical disease more slowly and have altered markers of systemic inflammation than wildtype mice, but ultimately develop colitis.
- Systemic injection of bioactive chemerin does not alter severity of DSS-induced inflammation (not shown).
- Considered altogether, bioactive chemerin is a novel biomarker for the severity of colitis.
- Strategies to modulate chemerin signaling other than chronic CMKLR1 loss are necessary to exploit chemerin as a therapeutic target for the treatment of IBD.

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