PERIOSTIN IN INFLAMMATORY BOWEL DISEASE (IBD) DEVELOPMENT AND SYNERGISTIC EFFECTS MEDIATED VIA CCL5

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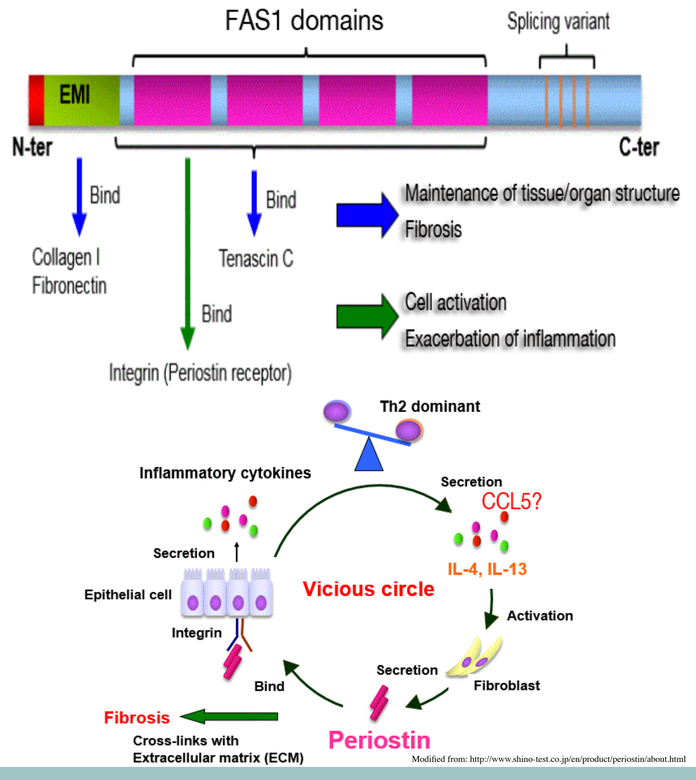
INTRODUCTION

The incidence of IBD is rising all over the world and is affecting 1 in 4000 people in Europe and 1 in 16.000 in Asia. [1] Well-documented, reliable numbers for Kazakhstan are currently not available but observations from local physicians (personal communication) suggest that numbers might be significantly higher than suggested by the literature. The matricellular protein Periostin has recently been shown to be involved in IBD [2] (and our own unpublished data). In a chemically induced murine model (dextrane sulfate sodium DSS) it mediates intestinal inflammation through the activation of NF-ϰB signaling, which suggests that periostin is a potential therapeutic target for inflammatory bowel disease [2]. CCL5, also know as RANTES, is a chemokine shown to be interacting with the G protein-coupled receptors CCR1, CCR3 and CCR5 [3]. In a recent study it could be shown that CCR5 expression correlates with the infiltration of inflammatory cells into the lamina propria of IBD patients [4].

Periostin is a matricellular protein originally isolated from osteoblasts and found to be preferentially expressed in the periosteum [5, 6]. Periostin contains an N-terminal secretory signal peptide, followed by a cysteine-rich domain, four internal homologous repeats, and a C-terminal hydrophilic domain. The four internal repeats exhibit homology to the axon guidance protein fasciclin I that is involved in the development of nervous system in invertebrates and were thus named fasciclin domains.

Structure/Function of periostin



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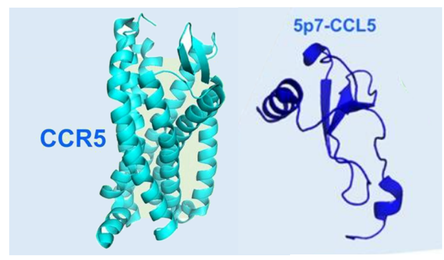
CCR5 & CCL5

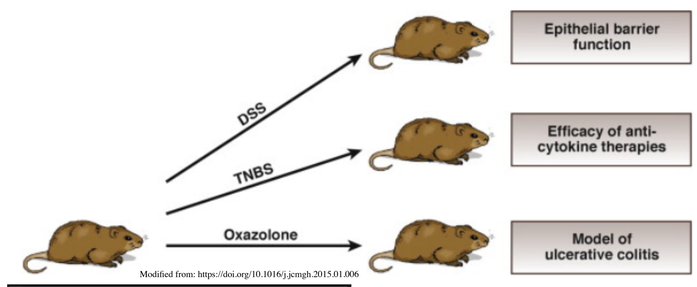
20 distinct chemokine receptors (CCRs) are currently known in humans. They are characterized by a 7-transmembrane (7TM) structure and couples to G-protein for signal transduction within the expressing cell, making them members of a large protein family of G protein-coupled receptors. Following interaction with their specific chemokine ligands, the chemokine receptors trigger a flux in intracellular calcium (Ca^{2+}) ions that causes cell responses, including chemotaxis that traffics the cell to a desired location within the organism. At least 10 types of CCRs can be detected in the gut and might be associated with IBD. Studies have shown that the CCR5 antagonists could alleviate the pathological changes and improve clinical symptoms by reducing leukocyte infiltration in experimental models of IBD.



Vangelista and his team showed in a recent report that by rational CCL5 mutagenesis they were able to generate an agonist and antagonist of very high activity [5].

Modified from The Expanding Therapeutic Perspective of CCR5 Blockade: Vangelista and Vento, Front Immunol. doi: 10.3389/fimmu.2017.01981

Mouse as a model



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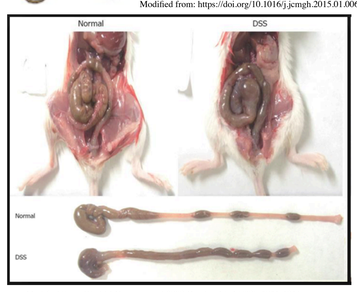


Modified from: World J Gastroenterol 2008 October 14; 14(38): 5851-5856

Disruption of the intestinal epithelial barrier and thereby the entry of luminal bacteria or bacterial antigens into the mucosa has been clearly established as a disease mechanism in enterocolitis by the fact that intestinal inflammation can be more easily induced or may occur spontaneously in numerous murine models characterized by molecular abnormalities that cause massive barrier loss.

Results: Immunohistochemistry on control and IBD tissue in humans with α-periostin

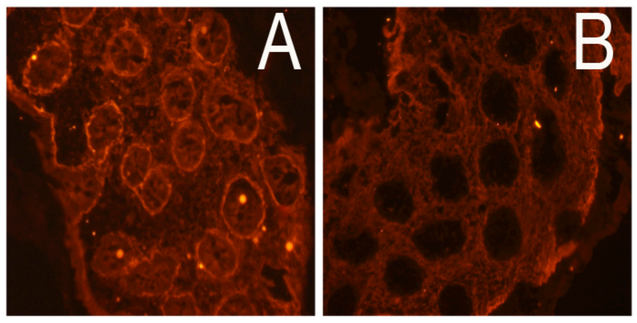
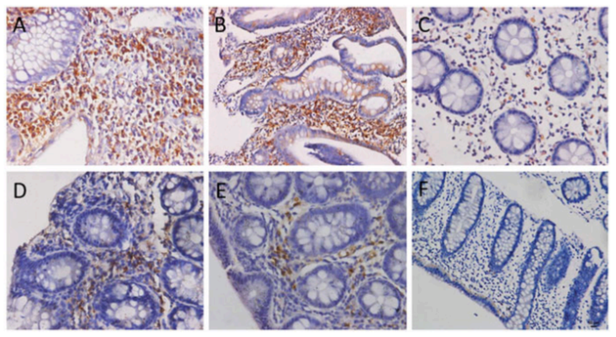


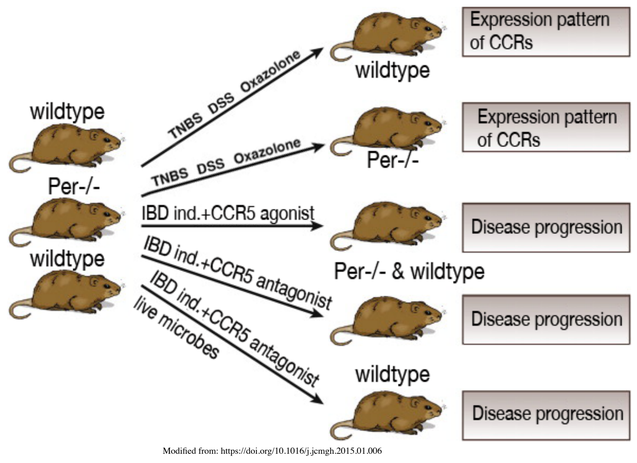
Fig. 1: Intestinal Periostin expression in IBD patients A and control patients B. Note the different pattern of expression and the increased intensity. A similar pattern can be observed in DSS induced murine tissue.

Results: Immunohistochemistry on different patients using α−CCR5



The expression of CCR5 in each group. (A) Strong positive expression of CCR5 in active Crohns Disease CD; (C) Weakly positive expression of CCR5 in remissive CD; (D) Weakly positive expression of CCR5 in the control; (F) Negative expression of CCR5 in the control. (Taken from Ye et al. [4]

Experimental design



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Chemical induction of IBD in mice using different agents and different conditions. Disease severity and progression will be closely monitored.

Hypothesis

Periostin has been shown to be involved in a variety of inflammatory processes and is in general exaccerbating the inflammation. Absence of Periostin in the IBD setting is protective as we and others have shown. CCR5 antagonists are known to alleviate the inflammatory process and thus negative side-effects. Whether Periostin and CCR5 sigalling is happening via the same route will be tested here.

Additionally the new variants of CCL5 will be tested in the IBD setting. It is expected that these molecules are highly active in-vivo and will be very potent.

Our expectation is that the absence of Periostin has an impact on MMPs and chemokine receptors and thus would open novel options for treatment by inhibiting these activities. In the second part of the project we will test the CCR5 antagonist as chemically synthesized protein [5] in-vivo in the DSS and other IBD models.

Outlook

1. Once the new variants have been confirmed to be active in the IBD setting the possibility to use live microbes expressing the antagonist will be tested in-vivo.

2. As absence of Periostin has an impact on IBD severity and progression inhibition of periostin-signalling as potential route for treatment of IBD will be exploited.

3. In case absence of Periostin has no impact on CCR5 expression (expected to lower expression) inhibition of periostin-signalling in combination with CCR5 blockage will be exploited as potential route for treatment of IBD.

REFEERENCES:

1. Molodecky, N.A., et al., Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology, 2012. 142(1): p. 46-54.
2. Koh, S.J., et al., Matricellular Protein Periostin Mediates Intestinal Inflammation through the Activation of Nuclear Factor kappaB Signaling. PLoS One, 2016. 11(2): p. e0149652.
3. Struyf, S., et al., Diverging binding capacities of natural LD78beta isoforms of macrophage inflammatory protein-1alpha to the CC chemokine receptors 1, 3 and 5 affect their anti-HIV-1 activity and chemotactic potencies for neutrophils and eosinophils. Eur J Immunol, 2001. 31(7): p. 2170-8.
4. Ye, X., et al., CCR5 expression in inflammatory bowel disease and its correlation with inflammatory cells and beta-arrestin2 expression. Scand J Gastroenterol, 2017. 52(5): p. 551-557..
5. Secchi, M., V. Grampa, and L. Vangelista, Rational CCL5 mutagenesis integration in a lactobacilli platform generates HIV-1 blockers of unprecedented activity. 2018 Sci. Rep 8 (1) 1890.
6. Horiuchi, K., et al., *Identification and characterization of a novel protein, periostin, with restricted expression to periosteum and periodontal ligament and increased expression by transforming growth factor beta*. J Bone Miner Res, 1999. **14**(7): p. 1239-49.