**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 400 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 The matricellular protein Periostin has recently been shown to be involved in IBD [2] (and our own unpublished data).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 (dextran 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 known 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 periostium [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 was thus named fasciclin domain.

**CCR5 & CCL5**

20 distinct chemokine receptors (CCRs) are currently known in humans. They are characterized by a 7-transmembrane (7TM) structure and couple 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 (Ca²⁺) 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.

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

![Immunohistochemistry on control and IBD tissue in humans with α-periostin](image1)

**Mouse as a model**

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 established as a disease mechanism in mice than in humans. They are characterized by a 7-transmembrane (7TM) structure and couple to G-protein for signal transduction within the organism.

**Hypothesis**

Periostin has been shown to be involved in a variety of inflammatory processes and is in general exacerbating 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 signaling is happening via the same route will be tested here.

**Results: Immunohistochemistry on different patients using α-CCR5**

![Immunohistochemistry on different patients using α-CCR5](image2)

**Structure/Function of periostin**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>FASl</td>
<td>Antigen presentation and cell adhesion</td>
</tr>
<tr>
<td>BASL</td>
<td>Basal lamina formation</td>
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</tbody>
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**Experimental design**

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

**Outlook**

1. Once the new variants have been confirmed to be active in the IBD setting the possibility to use live microspheres expressing the antagonist will be tested in-vivo.
2. An absence of Periostin has an impact on IBD severity and progression inhibition of periostin-signaling 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-signaling in combination with CCR5 blockage will be explored as potential route for treatment of IBD.

**REFERENCES**