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LETTER TO EDITOR

Chemerin, a novel player in inflammatory bowel disease

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Inflammatory bowel disease (IBD) manifests during Crohn's disease and ulcerative colitis as well as in a group of inflammatory disorders of the gastro-intestinal tract.[1] The etiology of IBD is thought to be a combination of genetics and environmental factors, including the microbiome and immune system of the individual.[1]

The initial immune response in the intestine is controlled by macrophages, dendritic cells and intestinal epithelial cells. Intestinal macrophages are pha-gocytic and bactericidal, but are mostly refractory to inflammatory stimulation. Microbes do not trigger the production of pro-inflammatory cytokines, prevent-ing an unfavorable response to resident commensal flora. These cells do not respond to Toll-like receptor ligands and express anti-inflammatory cytokines. In IBD, Toll-like receptor-responsive macro-phages that release pro-inflammatory cytokines arise.[2] Activated macrophages are commonly categorized as classically activated (M1-type) or alternatively acti-vated (M2-type). The latter are characteri-zed by the expression of arginase and the mannose receptor CD206.[2] However, due to the heterogeneity of tissue macro-phages, this categorization is simplified, and resident intestinal macrophages can-not be easily assigned to one of these classes.[2]

Mesenteric fat hypertrophy is a com-mon feature in IBD, particularly in Crohn's disease.[3] Proteins secreted by adipose tissue, such as adiponectin and leptin, regulate immune function, sug-gesting that increased synthesis of these proteins in adipose tissue and higher sys-temic levels in IBD may contribute to disease pathogenesis.[3] Chemerin, which is mainly expressed in adipocytes and hepatocytes, is also present at higher concentrations in serum from IBD patients.[4–6] Chemerin is an attractant for immune cells and may play a role in the recruitment of tissue macrophages.[4] Chemerin produced by human fetal intestinal epithelial cells constitutes most of the chemotactic macrophage activity observed in cultured fetal intestinal epi-thelial cells.[7] In mature intestine, small amounts of chemerin are expressed, sug-gesting that the postnatal attraction of immune cells is initiated by other che-mokines.[7]

Research on IBD commonly uses dex-tran sodium sulfate (DSS)-induced colitis in mice. Intestinal hyperpermeability affects the penetration of pathogens, toxic compounds and macromolecules. In this model, mucosal inflammation is main-tained by cells of the innate immune system.[8] Using this model, Lin and collea-gues[9] report that chemerin aggravates colitis. Importantly, intraperitoneal injec-tion of chemerin (aa16-157) strongly increases chemerin serum levels, but does not cause inflammation in healthy mice. Circulating chemerin is elevated in experimental colitis (Figure 1) and is fur-ther increased by intraperitoneal admin-istration of chemerin. Chemerin-treated mice display significantly greater weight

loss, colon shortening, and exaggerated histological damage, as well as a higher disease activity index at day 8 following DSS exposure. TNF and IL-6 serum levels and secretion by colonic cells are mar-kedly induced (Figure 1). Unexpectedly, chemerin administration does not affect the number of dendritic cells, neutrophils, macrophages and natural killer cells in the colon. RT-PCR expression analysis reveals a colitis-associated mRNA upregula-tion of the M2 genes, including arginase-1 and IL-10, which is completely abrogated by chemerin treatment (Figure 1).

The chemerin receptor CMKLR1 is expressed by macrophages, but not neu-trophils or dendritic cells, suggesting that this chemokine may directly affect macrophages function.[9] *In vitro* experi-ments using peritoneal macrophages demonstrate that (i) chemerin alone has no effect on the expression of the M2 genes analyzed; (ii) chemerin does not enhance lipopolysaccharide-mediated M1 activation, in agreement with recently published findings;[10] (iii) chemerin impairs IL-4-induced phos-phorylation of STAT6 and M2-induced macrophage polarization; and (iv) IL-4 upregulates expression of CMKLR1 by macrophages.

In mouse peritoneal macrophages, lipo-polysaccharide upregulates CMKLR1,[11] whereas a second study demonstrates that macrophage CMKLR1 is suppressed by inflammatory cytokines and Toll-like receptor ligands, such as lipopolysaccha-ride. The immune-suppressive cytokines TGF-beta[12] and IL-4 induce CMKLR1 expression.[9] Thus, further studies are needed to elucidate whether classically activated macrophages are less responsive

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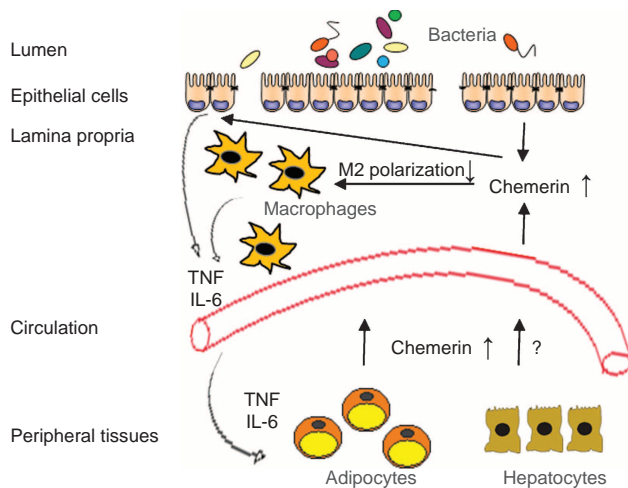Received: 10 February 2014; Accepted: 11 February 2014

Figure 1 Role of chemerin in dextran sodium sulfate (DSS) colitis. In DSS colitis, colonic epithelial cells release more chemerin. Chemerin enhances IL-6 and TNF secretion in these cells. It further blocks M2 polarization of macrophages, which is most likely associated with higher release of inflammatory cytokines. Increased pro-inflammatory cytokines in circulation might induce chemerin in mesenteric adipocytes and subsequently contribute to higher systemic levels. Whether chemerin in serum plays a role in the local effects in the bowel requires further study. Hepatocyte chemerin synthesis is not induced by inflammatory cytokines or lipopolysaccharide, suggesting that liver chemerin is not increased in inflammatory bowel disease.

to chemerin compared to alternatively activated cells.

To evaluate the contribution of endogenous chemerin to disease severity, an antibody blocking chemerin activity has been tested.[9] Administration of this antibody improves histological scores, but not the clinical manifestations of DSS colitis. Lin and colleagues[9] speculate that this approach does not efficiently block endogenous chemerin and suggest the use of chemerin knockout mice to perform confirmatory experiments. Despite this limitation, cultured colonic cells from antibody-treated mice produce lower levels of TNF. Furthermore, colonic expression of arginase-1 is induced. Again, the number of inflammatory cells is not affected. Collectively, these data demonstrate that chemerin has a role in IBD pathology.

Elevated systemic chemerin is, however, not related to disease activity in IBD patients.[6] In colon biopsies of patients with ulcerative colitis, the expression of chemerin is higher in inflamed tissues and, importantly, is further increased in more severely inflamed tissues.[9] Colon cells isolated from

DSS-treated mice release chemerin at levels consistent with disease severity. Therefore, only locally produced chemerin is associated with disease severity in rodent and human IBD.[6,9]

Higher circulating chemerin levels in IBD may result from increased intestinal or colonic secretion. Furthermore, pro-inflammatory cytokines induce adipocytes to express chemerin but have no effect on hepatocytes[4,5] (Figure 1). Overall, the study by Lin and colleagues demonstrates a role for chemerin in IBD pathophysiology in a commonly used rodent model.[9] CMKLR1 is induced in the colon tissue of DSS-treated mice[11] and serves as a receptor for chemerin and resolvin E1. Chemerin exacerbates[9] and resolvin E1 prevents DSS colitis,[11] and the underlying mechanisms of the opposing effects of these ligands still need to be characterized. Additional studies using different IBD models, other strategies to block endogenous chemerin action and experiments to reveal the role of chemerin in human IBD are needed before chemerin targeting can be used as a novel approach to treat IBD.

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