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Chemokines in colitis: microRNA control

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Huang *et al*[1] identified and tested the role of a specific microRNA (miRNA) in the pathogenesis of IBD. The study of microRNAs is a burgeoning field within epigenetics. These small non-coding RNAs mediate translation-level repression of protein expression by binding to the 3′-untranslated region of specific messenger RNA transcripts. In the innate and adaptive immune response, miRNAs play an important role in negative regulation of inflammatory conditions in the intestine. Inflammatory regulators such as IL-6, tumor necrosis factor (TNF) and toll-like receptors have been shown to induce miRNA expression in both acute and chronic inflammation. The roles for miRNAs in IBD are emerging from recent studies that compare miRNA expression in colonoscopic and peripheral blood draw biopsies from colitis patients with healthy individuals.[2] Despite this, the vast majority of miRNAs identified in microarray analyses of colitis patients have yet to be investigated in experimental models of colitis or assigned specific mechanisms in the pathophysiology of human disease. In a novel approach, Huang *et al*[1] used array analyses to assay changes in microRNA expression from two different experimental models of colitis in order to map specific overlapping miRNA expression patterns, which were subsequently compared against analyses completed on human colitis patient specimens. These authors then continued their analyses to mechanistically determine that miR-141, a miRNA aberrantly expressed in both animal models of colitis and human patients, specifically inhibited expression of the β-isoform of CXCL12, a chemokine known to regulate lymphocyte recirculation and participate in directed migration of leukocytes into mucosal tissues.[1]

Inflammation-induced miRNAs, such as miR-146a/b and miR-155, act as negative feedback regulators of inflammation in immune cells by repressing a myriad of immune factors, including IRAK, STAT3 and NF-κB.[3] This negative regulation leads to depressed expression of several proinflammatory factors including many inducible chemotactic

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Competing interests The use of recombinant CXCL12 as an antimetastatic drug is protected by US Patent 8 404 640 to MBD. BFV and MBD as co-founders of Protein Foundry, LLC, a manufacturer of molecular grade chemokines for use in biomedical research.

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cytokines (chemokines).[3] Recent studies of miRNAs regulating chemokine activity have shown cell type specific links between CXCL12 expression and progenitor cell differentiation and migration in the context of tissue injury repair,[45] or in endothelial cell expression during ischaemic injury.[6] While a multitude of chemokines are known to be upregulated during bouts of colitis in patients with either Crohn's disease or ulcerative colitis, roles for CXCL12 are decidedly more mixed. Despite its initial classification as a 'homeostatic' chemokine, reports show increased transcript levels of CXCL12, as well as its cognate receptor CXCR4, in IBD.[78] In contrast, we have shown little, if any, change in CXCL12 transcript or protein expression in patient samples or in cell culture model systems.[9] This is consistent with a paucity of NF-κB or AP1 transcription sites within the Cxcl12 promoter. Indeed, another group has shown that TNF is incapable of inducing CXCL12 expression in non-transformed cells.[10] The data by Huang and colleagues provide an alternative explanation for these discrepancies. Thus, their data suggest that alterations in the specific levels of CXCL12 transcript or protein may reflect changes in the levels of specific miRNAs dysregulated during the inflammatory response.

CXCL12 was first known as stromal cell-derived factor-1 for its abundant expression in the stromal cells of the bone marrow. It was independently characterised as pre-B cell growth factor for its ability to promote B cell proliferation. Genetic characterisation subsequently revealed the gene was variably expressed in a range of cell types and tissues, with pronounced expression in bone marrow and liver. Further, genetic analyses revealed alternatively spliced isoforms of the native protein. CXCL12α is encoded by a three exon transcript encoding a full-length 68-amino acid protein. The CXCL12β isoform possesses an additional four amino acids encoded on a fourth exon. In isolation, CXCL12α and CXCL12β are structurally similar proteins; protein nuclear magnetic resonance spectra indicate the CXCL12β isoform is identical to CXCL12α with the exception of signals arising from the C-terminal four amino acid extension. While CXCL12α and CXCL12β are structurally similar, the additional four amino acids of the CXCL12β molecule alter interactions with the cognate receptor and glycosaminoglycan chemokine-binding partners in a functionally significant manner. In particular, the C-terminal extension provides resistance to proteolysis by carboxypeptidase N,[11] increasing longevity of the secreted chemokine. In general, the half-life of CXCL12 is short, in the order of 0.5 s, unless the protein is stabilised by binding to glycosaminoglycans. Indeed, proteolysis of CXCL12α by carboxypeptidase N produces a 67-amino acid form of CXCL12 1–67, which is less effective at promoting chemotaxis or pre-B-cell proliferation than the intact α- or β-CXCL12 isoforms.[11] Huang and colleagues reveal a novel regulatory mechanism for CXCL12 function in which miR141 preferentially downregulates the β-CXCL12 and not the α-CXCL12 isoform, suggesting an alternative mechanism for controlling the expression levels of the chemokine. MicroRNA mediated suppression of the alternatively spliced and proteolytically stable β-isoform may therefore sculpt chemokine gradients with subsequent changes in its function within the tissue microenvironment.

Expression of CXCL12 and its receptor CXCR4 are maintained during gastrointestinal inflammatory disorders.[912] Given its nearly ubiquitous expression, the CXCR4 signalling axis may represent a fruitful target for therapeutic intervention. Indeed, both small molecule receptor antagonists such as plerixafor and genetic approaches of circularised CXCL12

plasmid DNA have progressed through Food and Drug Administration (FDA) approval and/or clinical trials. Plerixafor, a small molecule antagonist of the CXCL12 receptor CXCR4, showed pronounced efficacy in ameliorating DSS-induced colitis in a preclinical model.[13] As the chemokine receptor CXCR4 is a coreceptor for HIV, the drug was first used in clinical trials as an antiretroviral agent. However, in those trials where plerixafor was administered chronically as an antiretroviral agent, the compound demonstrated marked cardiotoxicity, suggesting its limited use as a therapeutic agent in IBD. Plerixafor was subsequently FDA-approved for acute use in bone marrow transplant settings. Given the limited use of plerixafor in a chronic setting, we investigated the potential use of the recombinant chemokine as a biological response modifier. In a series of studies, we demonstrated that recombinant CXCL12 administration disrupted hepatic metastasis of colon cancer cells in a preclinical model.[14] Ongoing studies seek to exploit the structure of CXCL12 and its receptor CXCR4 to control cellular movement in cancer and inflammation. Emerging evidence suggests that CXCL12β may play a dominant role in CXCR4-mediated cell migration in vivo,[15] a notion that is reinforced by this report in *Gut*.[1] Notably, with their work, Huang and colleagues demonstrated that in a preclinical mouse model setting, miR-141 therapy alleviated colitis through decreased CXCL12β expression and fewer immune cells infiltrating into the gut mucosa. Thus, future work may use epigenetic approaches to target specific isoforms of the chemokine to control its functions in health and disease.

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