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Building better bugs to deliver biologics in intestinal inflammation

Kim E Barrett

Despite intense effort, the inflammatory bowel diseases (IBDs) of ulcerative colitis and Crohn’s disease lack fully effective therapies for all patients. Current therapies include small molecules (anti-inflammatory agents and immunosuppressives) as well as biologics, which predominantly are antibody-based therapeutics that target specific facets of the inflammatory cascade, such as cytokines. Small molecule therapeutics suffer from their lack of specificity and thus the potential for significant side effects; this is particularly the case for systemic steroids, which remain the mainstay of therapy for many patients with severe IBD. Likewise, biologics, such as humanised antibodies that are directed against tumour necrosis factor α (TNFα), are expensive, require intravenous administration, and also suffer from the potential for side effects such as non-specific immunosuppression. Thus, in the absence of current information that would allow for a cure, patients with IBD are in great need of additional therapies that might modify their disease processes without a risk for unacceptable side effects.

To bypass some of the limitations associated with the use of biologic agents in IBD, some years ago, Steidler and colleagues published proof-of-principle experiments showing that probiotic micro-organisms could be engineered to express anti-inflammatory factors (in this particular example, the immunosuppressive cytokine interleukin 10 (IL10)), and that this could be shown to ameliorate bowel inflammation in an animal model of colitis. However, in these experiments it was not possible to control the luminal production of the therapeutic agent, and there were also concerns about environmental containment. Nevertheless, the work of Steidler and others implies that anti-inflammatory biologics, at least, might be supplied directly to the intestinal lumen to affect the outcome of IBD if these limitations could be overcome. Indeed, a preliminary clinical trial using this approach in Crohn’s disease has been reported.

The intestinal epithelium is also an appealing target for IBD therapy. Although current thinking about IBD pathogenesis implies that intestinal inflammation arises as an inappropriate immune response to the normal commensal microbiota resident in the gut, the epithelium is also a clear target of, and contributor to, perpetuation of the disease state. The intestinal epithelium is a key barrier that limits interactions between the mucosal immune system and the microbiota, as well as itself responding to luminal micro-organisms, when it is injured, with the production of chemokines and other factors that set up a vicious cycle of inflammation. Moreover, whether the epithelial barrier is compromised as a cause or a consequence of intestinal inflammation, there is now considerable evidence to suggest that restoring its barrier properties can interrupt the natural history of experimental intestinal inflammation, and thus serve as a basis for a lasting therapeutic effect in IBD. Among various strategies, the barrier properties of intestinal epithelial cells can be restored and/or augmented by administration of a variety of peptide growth factors, including epidermal growth factor, transforming growth factor α, and the keratinocyte growth factors (KGFs). Indeed, high doses of recombinant KGF-2, administered systemically, were shown to be effective in ulcerative colitis in short-term clinical trials, and epidermal growth factor (EGF) and growth hormone have also been shown to exert some therapeutic effects in this setting. Nevertheless, the observations with these growth factors face hurdles in wide-scale translation to therapeutic advances. First, as peptides, they have hitherto required intravenous delivery, to bypass luminal digestion. Second, systemic administration runs the risk of non-specific effects at extra-intestinal sites. Third, as biologics, they are expensive, particularly in the doses that are needed for a systemic effect. And finally, given their ability to stimulate epithelial proliferation, some have concluded that their use as therapeutic agents might be associated with an unacceptable risk of malignancy, a risk that is already amplified in patients suffering from intestinal inflammation.

In this issue of *Gut*, however, Hamady and colleagues (see page 461) present intriguing studies that deftly combine the use of a bacterial delivery vehicle for a complex biologic with an epithelial target for IBD therapy. They have engineered a human anaerobic commensal, *Bacteroides ovatus*, to express KGF-2. The anaerobic nature of the bacterium provides an inherent biosafety feature, as the organism should not survive outside the colon. Moreover, the work by Hamady and colleagues significantly extends prior efforts in that the production of KGF-2 by the engineered bacterium was regulated by placing its coding sequence under the control of the promoter for xylanase. Finally, *Bacteroides* spp. are known to associate with the mucus layer in the intestine, placing them in a niche where any of their secreted products would readily come into contact with an injured epithelium in the setting of colitis.

Using the engineered bacteria, the authors showed that production of KGF-2 was dramatically increased by exposure of the bacteria to xylan in vitro, or by administering xylan in the drinking water following infection of mice. Further, as expected, the bacteria were rapidly killed when exposed to environmental oxygen, suggesting that they would be unlikely to spread from the patients to whom they might ultimately be administered. Finally, the combination of the engineered bacteria plus xylan was impressively effective in reducing both histological and clinical evidence of disease in a standard mouse model of colitis. This clinical effect was not obtained to any meaningful degree with either the engineered bacteria alone, or with xylan administration in conjunction with wild-type bacteria. Importantly, moreover, efficacy was seen not only if the treatment was begun prior to the induction of colitis, but also once disease was established, implying the likelihood of effectiveness also in a clinical setting where long-term prophylaxis would be unlikely.
HIV protein gp120 and chemokines receptor for liver fibrosis

Gianluca Svegliati-Baroni, S De Minicis

Liver disease has become the second most common cause of death of HIV-infected patients,1 and the risk of liver-related death increases with progressive HIV-associated immunodeficiency.2 This observation allows for the possibility that the pathogenic mechanisms which promote T cell depletion may also promote liver injury. In HIV-infected patients, liver disease occurs most commonly from hepatitis C virus (HCV) infection, non-alcoholic steatohepatitis,4 as well as alcohol-associated liver disease occurs. Infection, HCV co-infection, active hepatitis B virus (HBV) infection, and how gp120 may interfere with hepatic stellate cells (HSCs), one of the subpopulation involved in liver fibrogenesis.3

Bruno et al (see page 513) have used an elegant approach to uncover an important new link between fibrogenic activity related to HSCs and HIV envelope protein gp120 (figure 1).7 They report that gp120 exerts profibrogenic action on humans HSCs in culture, identifying a direct pathway possibly linking HIV infection with liver fibrogenesis via envelope proteins. For the first time in the literature, the authors

Figure 1 gp120 activity on hepatic stellate cells (HSCs): schematic representation of the CCR5-mediated activation of phosphatidylinositol 3-kinase (PI3K) and nuclear factor-kB (NF-kB) signalling in HSCs, through the HIV envelope protein (gp120), in hepatitis C virus-infected individuals. IκBα, inhibitor of NF-kB; MCP-1, monocyte chemoattractant protein-1; RANTES, regulated on activation normal T cell expressed and secreted.