IBD

Role of interleukin 6 in a murine model of Crohn's ileitis: are cytokine/anticytokine strategies the future for IBD therapies?

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Although the precise causes of inflammatory bowel disease (IBD) have yet to be discovered, important therapeutic advances have resulted from the manipulation of cytokine function(s) using anticytokine/cytokine therapies, such as targeting of tumour necrosis factor. We discuss the future of this area of investigation in the context of preclinical experimentation using animal models of IBD. In particular, we pinpoint the roles played by interleukin 6 and its intracellular signalling pathways in the SAMP1/Yit murine model of Crohn's-like ileitis.

Over the past several years, a variety of animal models of inflammatory bowel disease (IBD) have been developed and investigated, with the ultimate goal of understanding the causes of Crohn's disease (CD) and ulcerative colitis (UC).^{1,2} Unfortunately, thus far no single animal model recapitulates all of the pathogenic and clinical features of human IBD, which has impeded our progress towards an understanding of the precise causes of these devastating diseases. Nevertheless, each animal model has provided us with a unique opportunity to advance our understanding of the mechanisms underlying initiation and perpetuation of chronic intestinal inflammation. This has allowed identification of novel targets in the disease process for potential therapeutic intervention. For instance, the explosion in the number of animal models of colitis based on gene deletion or overexpression has underlined the importance of cytokine gene products in gut immune regulation.³ Perhaps one of the best examples in this category is the interleukin (IL)-10 deficient mouse, which develops chronic enteritis, the characteristics of which are similar to human IBD.⁴ Despite the fact that no genetic or immunological abnormalities of the IL-10 pathway have been demonstrated in patients with IBD to date, this model has facilitated the development of therapeutic strategies based on administration of anti-inflammatory cytokines⁵ or delivery of regulatory T cells with anti-inflammatory activities.⁶

The SAMP1/Yit mouse model of ileitis, first described by Matsumoto and

colleagues,⁷ may represent a suitable model to investigate the aetiopathogenic mechanisms leading to IBD.⁸ Disease in this model is truly spontaneous, without the need for genetic, chemical, or immunological manipulation. None the less, the development of disease is dependent on both genetic and environmental factors, is mediated by lymphocytes and cytokines, and importantly, is responsive to conventional therapeutic agents that are effective in human IBD, including anti-tumour necrosis factor (TNF) and steroids.⁹ Discovering the precise mechanism of ileitis in these mice will likely allow a better understanding of the pathogenesis of CD, at least in the subgroup of patients who develop the terminal ileitis typical of this model. This will help drive the development of novel therapeutic strategies capable of significantly affecting the natural course of this disease. One of the problems with the use of this mouse model thus far has been the poor breeding abilities that are characteristic of this strain. However, at the present time, breeding pairs can be obtained from the Yakult Central Institute for Microbiology Research in Japan⁷ and experimental mice from the colony substrain developed at the University of Virginia.¹⁰ It is anticipated that widespread investigation and analysis of these mice will generate new and important information on the pathogenesis of CD, in particular disease affecting the small intestine, in the near future.

Despite the intrinsic limitations in our current understanding of the precise initiating factors of CD, there have been

significant advances in the therapeutic arena using biological therapies; in particular, monoclonal antibodies and fusion proteins that block the activity of proinflammatory cytokines.¹¹ In addition, local delivery of anti-inflammatory cytokines, such as IL-10,⁵ or administration of immunomodulatory cytokines, such as granulocyte macrophage-colony stimulating factor,¹² holds promise for future therapeutic options for CD. The most successful example in this arena has been the development of TNF-blocking agents, which are now widely employed in the treatment of both CD and UC. These agents have made a significant impact on the treatment of IBD patients, especially those affected by intestinal disease refractory to other anti-inflammatory and immunosuppressive drugs.¹³

In addition to TNF, other proinflammatory cytokine targets have been investigated in clinical trials, or are still under preclinical investigation but show promising preliminary results; examples of these include the Th1 cytokines interferon γ , IL-12, IL-23, and TLR1A, as well as the Th2 cytokines IL-4, IL-5, IL-13, and IL-21.^{11,14} Furthermore, rapid progress has been made in the study of cytokine biology, with 33 interleukins described at the present time. It is therefore anticipated that many more therapeutic strategies that modulate cytokine expression and function will be developed in the near future for the treatment of IBD.

Although cytokine and anticytokine therapies have not provided a cure for IBD, they have resulted in a dramatic improvement in the quality of life of patients with these chronic lifelong diseases.¹⁵ There is hope that advances in this field, particularly through the use of combination cytokine/anticytokine therapy, may allow the development of more effective therapies that will keep patients in "permanent remission", even if a complete cure is not achieved. In addition, it is still feasible that a "master" cytokine that is directly involved in the initiation of chronic intestinal inflammation in IBD may be identified. Nevertheless, it is important to consider the possibility of increased side effects due to the potent immunomodulatory actions of these cytokines and the potential immunosuppression resulting from their blockade. Reactivation of latent tuberculosis and the possibility of increased incidence of malignancy following long term suppression of TNF are examples of unwanted consequences of cytokine/anticytokine therapy.^{11,16}

The recent article by Mitsuyama *et al* published in this issue of the journal,¹⁷ explores the role of another important

Figure 1 Interleukin 6 (IL-6) can bind to both the soluble (s) and membrane bound (m) forms of the IL-6 receptor (IL-6R). On binding of IL-6, both forms of IL-6R can activate gp130 and subsequent downstream signalling pathways. The classic activation pathway (A) involves dimerisation of membrane bound IL-6R with gp130. (B) In tissues where membrane bound IL-6R is not expressed, soluble IL-6R (sIL-6R) can trigger gp130. This trans-signalling is therefore responsive to localised concentrations of sIL-6R. When triggered, gp130 activates Janus kinase (JAK) receptor associated kinases, which phosphorylate gp130 and thereby regulate the activity of STAT1/3 and the SHP2 cascade. Among other effects, this triggers negative regulators of these signalling pathways, including suppressor of cytokine signalling (SOCS)-1 and SOCS3. (C) Soluble gp130 (sgp130) can bind to sIL-6R and prevent its interaction with membrane bound gp130. This effectively prevents activation of gp130 and subsequent downstream signalling events.

cytokine implicated in the inflammatory response (that is, IL-6) (*see page 1263*). A number of studies have already investigated the role of IL-6 in both animal models of intestinal inflammation and patients with IBD. In fact, blockade of IL-6 in a mouse model of immunologically mediated colitis was able to prevent disease.¹⁸ In addition, IL-6 has been implicated in the regulation of lamina propria mononuclear cell apoptosis in both human and experimental colitis.¹⁹ Finally, in a preliminary clinical trial, an IL-6 inhibitory molecule induced a clinical response in 80% of patients with CD.²⁰ The study reported by Mitsuyama *et al* takes these findings a step further, and shows that a transcription factor, signal transducers and activators of transcription (STAT)-3, mediates the proinflammatory effects of IL-6 in ileitis in SAMP1/Yit mice. This transcription factor is part of the complex intracellular signalling cascade activated by IL-6 on target effector cells (fig 1). Taking advantage of our improved understanding of the mechanisms involved in IL-6 signalling, the authors elegantly show that administration of "hyper IL-6" (a complex of IL-6/IL-6 receptor) increased the severity of ileitis in SAMP1/Yit mice, whereas treatment with an IL-6 inhibitor (soluble

gp130-Fc) ameliorates the severity of gut inflammation in this model. Both interventions appear to modulate phosphorylation of STAT3, which mediates the activity of IL-6 during the pathogenesis of ileitis in SAMP1/Yit mice.

Studies such as this one, which investigate the molecular mechanism(s) of cytokine blockade in experimental CD, help us to better understand the actions of proinflammatory cytokines such as IL-6 at the cellular level, as well as to develop more targeted interventions with decreased immunosuppressive and deleterious side effects. One remarkable observation made by the authors is the ability of IL-6 blockade to suppress ileitis in SAMP1/Yit mice, which is similar to the reported beneficial effects in CD. This adds another treatment modality to the list of those that are effective in both SAMP1/Yit mice and human IBD, reinforcing the validity of SAMP1/Yit as a model of this disease. It will be very interesting to see whether the positive results from the pilot clinical trials, reported in 2004 by Ito and colleagues,²⁰ will be reproduced in larger multicentre trials in Europe and North America.

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REFERENCES

- Pizarro TT, Arseneau KO, Bamias, *et al*. Mouse models for the study of Crohn's disease. *Trends Mol Med* 2003;**9**:218–22.
- Strober W, Fuss IJ, Blumberg RS. The immunology of mucosal models of inflammation. *Annu Rev Immunol* 2002;**20**:495–49.
- Bahn AK, Mizoguchi E, Smith RN, *et al*. Colitis in transgenic and knockout animals as models of human inflammatory bowel disease. *Immunol Rev* 1999;**169**:195–07.
- Kuhn R, Lohler J, Rennick D, *et al*. Interleukin-10-deficient mice develop chronic enterocolitis. *Cell* 1993;**75**:263–74.
- Steidler L, Hans W, Schotte L, *et al*. Treatment of murine colitis by *Lactococcus lactis* secreting interleukin-10. *Science* 2000;**289**:1352–5.
- Coombes JL, Robinson NJ, Maloy KJ, *et al*. Regulatory T cells and intestinal homeostasis. *Immunol Rev* 2005;**204**:184–94.
- Matsumoto S, Okabe Y, Setoyama H, *et al*. Inflammatory bowel disease-like enteritis and caecitis in a senescence accelerated mouse P1/Yit strain. *Gut* 1998;**43**:71–8.
- Strober W, Nakamura K, Kitani A. The SAMP1/Yit mouse: another step closer to modeling human inflammatory bowel disease. *J Clin Invest* 2001;**107**:667–70.
- Kosiewicz MM, Nast CC, Krishnan A, *et al*. Th1-type responses mediate spontaneous ileitis in a novel murine model of Crohn's disease. *J Clin Invest* 2001;**107**:695–702.
- Rivera-Nieves J, Bamias G, Vidrich A, *et al*. Emergence of perianal fistulizing disease in the SAMP1/YitFc mouse, a spontaneous model of chronic ileitis. *Gastroenterology* 2003;**124**:972–82.
- Cominelli F. Cytokine-based therapies for Crohn's disease—new paradigms. *N Engl J Med* 2004;**351**:2045–8.
- Korzenick JR, Dieckgraefe BK, Valentine JF, *et al*. Sargramostim for active Crohn's disease. *N Engl J Med* 2005;**352**:2193–201.
- Rutgeerts P, Van Assche G, Vermeire S. Optimizing anti-TNF treatment in inflammatory bowel disease. *Gastroenterology* 2004;**126**:1593–610.
- Feagan BG, Yan S, Bala M, *et al*. The effects of infliximab maintenance therapy on health-related quality of life. *Am J Gastroenterol* 2003;**98**:2232–8.
- Sandborn WJ, Loftus EV. Balancing the risks and benefits of infliximab in the treatment of inflammatory bowel disease. *Gut* 2004;**53**:780–2.
- Isaacs KL, Lewis JD, Sandborn WJ, *et al*. State of the Art: IBD Therapy and Clinical Trials in IBD. *Inflamm Bowel Dis* 2005;**11**(suppl 1):S3–12.
- Mitsuyama K, Matsumoto S, Rose-John S, *et al*. STAT3 activation via interleukin 6 trans-signalling contributes to ileitis in SAMP1/Yit mice. *Gut* 2006;**55**:1263–9.
- Yamamoto M, Yoshizaki K, Kishimoto T, *et al*. IL-6 is required for the development of Th1 cell-mediated murine colitis. *J Immunol* 2000;**164**:4878–82.
- Atreya R, Mudter J, Finotto S, *et al*. Blockade of interleukin 6 trans signaling suppresses T-cell resistance against apoptosis in chronic intestinal inflammation: evidence in Crohn's disease and experimental colitis in vivo. *Nat Med* 2000;**6**:583–8.
- Ito H, Tazawa M, Fukuda Y, *et al*. A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. *Gastroenterology* 2004;**126**:989–96.