IL-22's gut feeling

By Peter A. Rittenhouse, Senior Writer

Although interleukin-22 has been implicated in several autoimmune and inflammatory diseases, figuring out how to use it as a target or a therapeutic has been challenging because of its contradictory roles in different tissues—sometimes even in the same tissue. Researchers at **Massachusetts General Hospital** and **Harvard Medical School** reported in the *Journal of Clinical Investigation* a new role for interleukin-22 in promoting mucus secretion from the colon and have developed a localized delivery method that may allow the cytokine to be used to treat ulcerative colitis without upsetting its function in other tissues.¹

Interleukin-22 (IL-22) is produced by Th17 cells, a subpopulation of CD4⁺ T helper cells named for one of their activities: the production of IL-17. IL-22 activates the transcription factors signal transducer and activator of transcription 1 (STAT1) and signal transducer and activator of transcription 3 (STAT3), which in turn activate genes involved in immune and inflammatory responses. IL-22 receptors are found on a number of

peripheral tissues including liver, gut, lung, spleen and skin¹⁻³ (see **Figure 1**, “Physiological effect of IL-22 on skin, colon and liver tissues”).

One problem with intervening in the IL-22 pathway is that the cytokine has proinflammatory properties in some tissues, protective properties in others and sometimes both in the same tissue.

“The biology of IL-22 is very complicated,” Wenjun Ouyang, a senior scientist at **Genentech Inc.**, told *SciBX*. “While it may play a pathogenic role in one disease, it can exert protective functions in other diseases. To make things even more complicated, other IL-22-family cytokines, such as IL-19, IL-20 and IL-24, share similar biological functions. It will be critical and a challenge to identify the right therapeutic approaches.”

Ouyang’s team at Genentech reported in *Nature* last year that in mouse ear skin, IL-22 promoted hyperplasia of the epidermis, which led to inflammation.³ They noted that IL-22 “mediates the crosstalk between the immune system and epithelial cells,” and concluded that better understanding of the Th17–IL-22 pathway might lead to discovery of new targets for the treatment of psoriasis.

In January, scientists at Wyeth Research (a division of **Wyeth**) using a similar model found that mice receiving anti-IL-22 antibodies did not develop epidermal inflammatory infiltrates.⁴ The authors concluded that “IL-22 antagonism might be a promising therapy for the treatment of human psoriasis.”

Figure 1. Physiological effect of IL-22 on skin, colon and liver tissues. Interleukin-22 (IL-22) mediates its effects through stimulation of signal transducer and activator of transcription-3 (STAT3) in the skin, colon and liver, as well as through protein kinase B (PKB; Akt) in the liver. By binding to its receptor, which is composed of the IL-22 receptor (IL-22R) and the IL-10 receptor (IL-10R), IL-22 activates tyrosine kinase receptor-2 (TYK2) and Janus kinase-1 (JAK-1), ultimately leading to the activation of STAT3; the binding of IL-22 to its receptor also starts the signaling cascade that leads to the activation of Akt.

STAT3 can activate many diverse processes involved in immunity, wound healing and cell survival. In the skin, hyperplasia, a critical component of psoriasis, is mediated through STAT3 activation. By contrast, in the colon, inflammation is attenuated by STAT3 activation, as lipopolysaccharides become bound by lipopolysaccharide-binding protein (LBP) and mucus-barrier formation is enhanced by production of mucin proteins (MUC1, MUC3, MUC13). In the liver, STAT3 activates antiapoptotic factors such as Bcl-2 and Bcl-XL, which in turn upregulate the acute-phase proteins serum amyloid A (SAA), antichymotrypsin (ACT; SERPINA3) and haptoglobin (HP). Additionally, activation of the Akt pathway in the liver promotes cell survival and opposes apoptosis through a variety of mechanisms.

ZymoGenetics Inc. was investigating the development of IL-22-receptor antagonists for the treatment of psoriasis. In 2004, ZymoGenetics granted exclusive, worldwide licenses to Serono S.A. to develop and commercialize products based on the IL-22 receptor. With the purchase of Serono by **Merck KGaA** in 2007, licensing for the IL-22-receptor antagonists has been transferred to **Merck Serono S.A.**, where it is under development.

On the flip side, researchers at **Yale University School of Medicine** reported in *Immunity* that mice deficient in IL-22 were highly susceptible to hepatic inflammation, suggesting a protective role for the cytokine in hepatitis.⁵ The group noted that “IL-22 receptor expression is absent on immune cells, but is instead restricted to the tissues, providing signaling directionality.” This differential expression is a big reason that IL-22 could be an attractive target.

Such studies clearly indicate that a therapeutic approach involving IL-22 would have to be tissue targeted, because a systemic approach would probably protect one tissue type from inflammation but promote inflammation in another tissue type.

However, even in a given organ system, previous papers have shown that IL-22 can have opposing roles, as in inflammatory bowel disease. The contrasting roles come from IL-22's downstream target, STAT3, which has the ability to enhance or suppress immune responses depending on its cellular location. For example, STAT3 can activate acquired immune T cell responses to promote the pathogenesis of colitis, or it can activate innate immune responses in colonic epithelial cells and macrophages, which help to diminish the inflammation associated with colitis.

Therefore, to be an effective therapy for ulcerative colitis (UC) that could relieve inflammation and promote healing of the colon, IL-22 would have to be selectively delivered to colonic epithelial cells that have innate immune functions.

In the *JCI* paper, the researchers tested numerous IL-22 gene-delivery approaches and found that the best system and route of administration were a nonmicrobial vehicle consisting of vector, lipid carrier and DNA-condensing agent microinjected directly into the colonic mucosa. In a mouse model of Th17-mediated colitis, direct delivery of IL-22 into the mucosa significantly reduced inflammation. Overexpression of IL-22 in the inflamed colon reduced colonic diameter within two weeks.

The group also found that IL-22 promoted induction of the *MUC1*,

MUC3 and *MUC13* genes. *MUC* genes regulate mucus-layer formation, and the authors suggest IL-22 is “a unique cytokine capable of enhancing mucus production by colonic epithelial cells through activation of STAT3.”

Although an increase in mucus secretion would likely benefit UC patients, the duration of the effect is not yet known. In the mice, mucus production diminished by four weeks after injection. Indeed, Atsushi Mizoguchi, one of the study's authors and an assistant professor of pathology at Massachusetts General Hospital, told *SciBX* that because the “induced expression of IL-22 by the gene delivery is transient, we are currently pursuing additional studies to see how long the therapeutic effect is preserved.”

Looking ahead, Mizoguchi said, “in humans, such microinjection delivery of IL-22 gene therapy may be performed through the procedure used in endoscopic mucosal resection,” which such patients would probably need in any case depending on the severity of the disease. What is not yet clear is whether patients would need repeat endoscopic mucosal resection injections. Because the lipid carrier used for the gene delivery is commercially available, a patent for this delivery system was not considered.

The fact that the vector is nonmicrobial should limit unwanted immune responses to it. However, potential adverse effects of the lipid-carrier system still need to be ruled out.

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