Researchers find link between inflammation, tissue regeneration and wound repair response

25 February 2015

Almost all injuries, even minor skin scratches, trigger an inflammatory response, which provides protection against invading microbes but also turns on regenerative signals needed for healing and injury repair - a process that is generally understood but remains mysterious in its particulars.

Writing in the February 25 online issue of *Nature*, an international team of scientists, headed by researchers at the University of California, San Diego School of Medicine, report finding new links between inflammation and regeneration: signaling pathways that are activated by a receptor protein called gp130. "We found that gp130 is capable of activating several signaling pathways that turn on a number of transcription factors known to have a key role in stem cell biology," said the study's lead author, Koji Taniguchi, MD, PhD, assistant project scientist in the Department of Pharmacology at UC San Diego.

These transcription factors - specifically STAT3, YAP and Notch - stimulate the proliferation and survival of normal tissue stem cells, which lead to healing and repair, said senior author Michael Karin, PhD, Distinguished Professor Pharmacology and Pathology and head of UC San Diego's Laboratory of Gene Regulation and Signal Transduction.

"While the work was mainly conducted on a mouse model of intestinal injury, similar to the one that underlies human inflammatory bowel disease (IBD), we provide evidence that the same mechanism may control liver regeneration, which suggests a general role in tissue repair," said Karin.

In addition to explaining a key biomedical phenomenon, the researchers said the findings have important clinical implications for the treatment of IBD and colorectal cancer. The major signal sensed by gp130 is the inflammatory hormone (cytokine) IL-6 and closely related proteins. Expression of IL-6 has been found to be elevated in IBD, both in Crohn's disease and ulcerative colitis, giving rise to the possibility that inhibition of IL-6 binding to its receptor - a complex between gp130 and a specific IL-6 binding protein - may ameliorate the pathology of IBD.

But just the opposite has been observed. Drugs that block the binding of IL-6 to its receptor complex actually increase the risk of intestinal perforation and bleeding, making them unsuitable for the treatment of IBD. The new work suggests that IL-6 and the signaling pathways it stimulates are not the cause of IBD, but are part of the natural protective reaction to the initial injury and inflammatory response associated with the onset of IBD.

The Taniguchi and Karin team say it is important that future treatments not interfere with the healing response triggered by IL-6 and gp130. Nonetheless, the same pathways involved in healing and regeneration can go awry and become chronically stimulated in colorectal cancer.

The new work defines several molecular targets suitable for development of new targeted therapies for this very common malignancy - the third leading cause of cancer-related death, though Karin cautioned that "such treatments should not be combined with conventional and highly toxic anti-cancer drugs whose major side effect is damage and inflammation of the intestinal mucosa, a disease known as mucositis that will only be exacerbated by blocking the regenerative response triggered by IL-6."