Boosting hedgehog against IBD

By Lauren Martz, Staff Writer

Researchers at **The University of Edinburgh** have identified a reduced-function variant of a protein in the hedgehog signaling pathway that could be targeted to treat irritable bowel diseases, including ulcerative colitis.¹ Although restoring the function of glioma-associated oncogene homolog 1 could lower inflammation in the colon, agonizing the pathway may also have malignant consequences because it is often upregulated in cancers.

The hedgehog signaling pathway is necessary for embryonic development and homeostasis for vertebrates. Previous studies by the Edinburgh team implicated the pathway in gut development, homeostasis and malignant transformation² and showed that glioma-associated oncogene homolog 1 (GLI1) was downregulated in intestinal mucosa from patients with ulcerative colitis (UC) compared with what was seen in noninflamed samples.³ However, hedgehog signaling had not been directly linked to irritable bowel disease (IBD).

Those hints, coupled with the cycle of inflammation, injury and repair associated with IBD, led the researchers to suggest that dampened hedgehog signaling could be essential for initiating the disease.

In a paper published in *PLoS Medicine*, Charles Lees and colleagues at Edinburgh identified a germline variation in *GLI1* that limited its function and therefore lowered pathway signaling. Lees is a clinical lecturer in gastroenterology in the Gastrointestinal Unit at the university's Centre for Molecular Medicine.

Genomewide haplotype tagging in three independent populations of Northern European IBD patients and healthy volunteers showed that the *GLI1* variant, dubbed *Q1100E*, was significantly associated with colitis in British and Scottish patients ($p < 0.0001$). The association was less pronounced in a Swedish population.

To determine the specific effects of lower *GLI1* activity, the team developed mice expressing only one copy of the gene, which resulted in Gli1 levels roughly 50% of those in wild-type mice. In the transformed animals, dextran sodium sulfate-induced colitis caused more severe intestinal inflammation, upregulated inflammatory cytokines IL-12, IL-17 and IL-23, and increased mortality compared with what was seen in littermate controls.

The findings suggest that decreased GLI1 activity increases inflammatory response to stress signals and susceptibility to UC. Thus, Lees told *SciBX*, "it is anticipated that agonizing the hedgehog signaling pathway would be beneficial to patients with inflammatory bowel disease."

His lab has not yet tested this hypothesis, but plans to test hedgehog agonists in animal models of colitis.

Treatment strategies

Compared with current IBD treatments, researchers think targeting GLI1 could prevent intestinal inflammation rather than treat the inflammatory response once it has been established.

Marketed IBD drugs include steroids and biologics such as anti-tumor necrosis factor antibodies. The former are not disease modifying, whereas the latter are expensive and come with a host of side effects such as infection and cancer.⁴

"The presently available treatments lack efficacy, have unwanted toxicities and poor patient compliance," said Lees.

"The strategy treats inflammation but intervenes further upstream to prevent the release of cytokines, compared with biologics or corticosteroids, which try to reduce cytokines once they are produced," said Lidia Demchyshyn, associate director of preclinical research at **NPS Pharmaceuticals Inc.**

NPS's Gattex teduglutide, an analog of glucagon-like peptide 2 (CGC; GLP-2), is in Phase II testing to treat Crohn's disease and in Phase III testing to treat short bowel syndrome.

Demchyshyn noted that the Edinburgh researchers detected a change in charge in the *Q1100E* variant near the domain that induces gene expression. Thus, she said, compounds could be developed that "avoid the change in charge that occurs and causes the reduced activity of the protein."

Marcel Miampamba, principal scientist of discovery biology at **Ardea Biosciences Inc.**, said the options for therapeutic intervention include potentiating the ability of GLI1 to induce gene expression, neutralizing the reduced-activity protein using an antibody or anti-sense molecule and then administering intact GLI1, or supplementing UC patients with exogenous GLI1 to stimulate the hedgehog signaling pathway's anti-inflammatory effects.

Ardea's RDEA119, a selective inhibitor of mitogen-activated ERK kinase (MEK), is in preclinical testing to treat UC.

Lees said an essential next step is to evaluate a general hedgehog agonist *in vivo* for proof of principal. "However, it is anticipated that more specific targeting of intestinal hedgehog signals will be required due to the wide-ranging effects of hedgehog in diverse organs and tissues," he said.

Selective relief

In addition to showing proof of concept and developing gut-specific hedgehog agonists, another challenge in translating the Edinburgh findings to the clinic will be identifying the right patients.

"The variant occurs in subpopulations. In Scotland and England, they saw a strong correlation, but the correlation was not as strong in the Swedish population," noted Demchyshyn. "Therefore, normalization of hedgehog signaling might not work in all patients."

Lees, however, thinks restoring GLI1 activity or upregulating hedgehog signaling could benefit a population beyond those with

the specific variant. “A large body of evidence now indicates that decreased hedgehog pathway activity, and specifically GLI1, is associated with intestinal inflammation. We see a downregulation of GLI1 in human IBD, even in patients without the specific variant,” he said.

Although increasing GLI1 activity might not have a direct benefit in all patients, Demchyshyn did say it could help patients with other problems in the hedgehog signaling pathway. For example, she said, “if you have an inability to bind hedgehog to PTCH, which is upstream of GLI1 in the hedgehog signaling pathway, it would be possible that GLI1 could enhance hedgehog signaling by directly bypassing that step.”

Demchyshyn added that the GLI1 variant offers the benefit of easy identification of patients who will respond through a simple blood test designed to detect it.

Balancing act

Regardless of which patient populations would benefit from agonizing GLI1, there was consensus that hedgehog agonists need to be monitored for cancer-inducing side effects. Overactivation of the hedgehog pathway has been documented in many cancers,⁵ including a recent report of GLI1 activation in pancreatic ductal adenocarcinoma cells.⁶

Multiple companies are pursuing hedgehog antagonists, including partners **Curis Inc.** and **Genentech Inc.**, which are running Phase II studies of GDC-0449 for first-line metastatic colorectal cancer, advanced basal cell carcinoma and advanced ovarian cancer. Also, **Infinity Pharmaceuticals Inc.** is running a Phase I trial of its IPI-926 to treat solid tumors.

Lees said that in the planned preclinical testing, his team will be looking for any evidence of procarcinogenic effects of hedgehog agonists.

“There is a fine line that you see when you start looking at development pathways, particularly here in the intestine, between homeostasis and malignancy,” said Demchyshyn. “You need to determine how much intervention in the pathway is necessary to maintain that balance.”

Lees said the research has not been patented and is not available for licensing.

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Contact: Deborah L. Gumucio, University of Michigan Medical School, Ann Arbor, Mich.
e-mail: dgumucio@umich.edu
Contact: Charlie W. Lees, University of Edinburgh, Edinburgh, U.K.
e-mail: Charlie.lees@ed.ac.uk
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COMPANIES AND INSTITUTIONS MENTIONED

Ardea Biosciences Inc. (NASDAQ:RDEA), San Diego, Calif.
Curis Inc. (NASDAQ:CRIS), Cambridge, Mass.
Genentech Inc. (NYSE:DNA), South San Francisco, Calif.
Infinity Pharmaceuticals Inc. (NASDAQ:IFNI), Cambridge, Mass.
NPS Pharmaceuticals Inc. (NASDAQ:NPSP), Bedminster, N.J.
The University of Edinburgh, Edinburgh, U.K.