Unique pathway in diabetes

By Lev Osherovich, Senior Writer

A North American team has identified a proinflammatory pathway involving eukaryotic translation initiation factor 5A, a poorly understood translational initiation factor, as a potential player in diabetes.¹ Senesco Technologies Inc., which collaborated on the study, has a pancreas-specific formulation of a eukaryotic translation initiation factor 5A small interfering RNA in preclinical development for diabetes. Cytokine PharmaSciences Inc. has a Phase II-ready anti-inflammatory compound that may also block the pathway.

Eukaryotic translation initiation factor 5A (EIF5A) is “somewhat enigmatic, in that we haven’t understood what its normal role is,” said Raghavendra Mirmira, professor of pediatrics and medicine at the Indiana University School of Medicine. He is the corresponding author on the paper in *The Journal of Clinical Investigation* that describes the findings.

EIF5A undergoes a unique post-translational modification in which a single lysine residue is converted into an unconventional amino acid called hypusine that is found nowhere else in nature. This conversion requires the sequential activity of two enzymes: deoxyhypusine synthase (DHPS) and deoxyhypusine hydroxylase/monooxygenase (DOHH).

Although mouse knockouts have shown that Eif5a hypusination is not essential for survival under most circumstances, work published in 2008 suggested that Eif5a promoted lung inflammation and sepsis in mice.²

Because many proinflammatory pathways are at play in the pancreas in both type 1 and type 2 diabetes, the researchers hypothesized that EIF5A might also contribute to pancreatic inflammation.

Indeed, Mirmira’s study now suggests that EIF5A mediates stress-induced inflammation in the pancreas, and it adds to growing evidence of an inflammatory component to both type 1 and type 2 diabetes that exacerbates islet β cell destruction.³

“We see this pathway as a potential therapeutic target in inflammatory diseases including diabetes, where EIF5A’s activity promotes the demise” of islet β cells, Mirmira told SciBX.

The team included researchers from the University of Virginia, Eastern Virginia Medical School, the University of Waterloo, Senesco and the University of Colorado Health Sciences Center.

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—Raghavendra Mirmira,
Indiana University
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Inflammation translation

The team first showed in a mouse model of diabetes that siRNA knockdown of Eif5a reduced islet cell loss and improved glucose tolerance compared with what was seen using control siRNA or no treatment.

EIF5A promoted inflammation by stimulating the translation of mRNA encoding inducible nitric oxide synthase (NOS2; iNOS), an intracellular effector of inflammation-associated cell death. EIF5A knockdown in mice and cultured human islet β cells reduced levels of iNOS compared with those seen using control siRNA or no treatment.

The team then tested whether hypusination was required for EIF5A’s effects on inflammation. The team found that a commercially available small molecule inhibitor of DHPS blocked the translation of iNOS, glucose response and insulin secretion in cultured β cells.

Diabetic mice treated with the DHPS inhibitor had lower iNOS and inflammatory cytokine levels and better glucose tolerance and insulin secretion than untreated controls.

To explain why blocking EIF5A hypusination should prevent both production of inflammatory cytokines and iNOS translation, Mirmira suggested that the pathway could be active in a variety of cell types.

“EIF5A is active in both islet cells and inflammatory cells,” said Mirmira. “There is signaling through this pathway going on in the β cells, but there may be an additional benefit to inhibiting the process in the immune cells.”

Mirmira next plans to test the effect of both blocking EIF5A hypusination in other models of diabetes and combining hypusination-blocking compounds with anti-inflammatory molecules that target other pathways.

Pick a target

Mirmira thinks the best target in the pathway may be DHPS and has filed a use patent on inhibiting the enzyme to treat inflammatory disease. The IP is available for licensing from the University of Indiana.

“There is very good evidence that this is a druggable target,” said Mirmira. “There are crystal structures of the enzyme and specific inhibitors” available as research reagents that could potentially be a starting point for medicinal chemistry efforts.

In addition, Mirmira noted that Cytokine’s compound semapimod inhibits DHPS *in vitro*. He suggested his findings could potentially explain that compound’s anti-inflammatory effects.

Semapimod (CNI-1493) has undergone Phase II testing for psoriasis, Crohn’s disease and endoscopy-induced pancreatitis.

Vidal de la Cruz, VP of business development at Cytokine, said Mirmira’s findings could highlight one of several possible mechanisms reported for semapimod, an anti-inflammatory compound.

“That’s not the only mechanism reported for semapimod,” said de la Cruz. “This compound was initially thought to be a p38 MAP kinase inhibitor,” but subsequent studies by the company and academics have identified another kinase as the potential target for its anticytokine activity. Another reported activity of the drug is stimulation of the vagus nerve, de la Cruz added.

He also said Cytokine is developing a highly active oral formulation of semapimod, known as CPSI-2364, and hopes to start a Phase II trial of that compound in Crohn's disease this year.

The company has tested the new semapimod formulation in "various animal models, including type 2 diabetes, with positive results," de la Cruz added.

Richard Dondero, VP of R&D at Senesco and a coauthor on the *JCI* paper, said that although hypusination of EIF5A by DHPS is critical for inflammation, EIF5A itself may be the better target.

The findings show that "in inflammation, the hypusinated form of EIF5A leads to cytokine production," said Dondero, whereas in cancer "the hypusinated form promotes survival."

Dondero noted that in the absence of hypusination, EIF5A instead triggers apoptosis. Thus, blocking hypusination is part of Senesco's cancer therapy strategy, which involves siRNA knockdown of native EIF5A while expressing a transgenic form of the protein that cannot undergo hypusination.

The company's SNS-01T, a combination EIF5A-targeting siRNA and a plasmid encoding a hypusination-resistant form of EIF5A, is in Phase I/II testing to treat multiple myeloma (MM).

Dondero said systemic inhibition of hypusination by targeting DHPS or DOHH could lead to accumulation of the proapoptotic form

of EIF5A, which "may not be desirable." In contrast, he said, localized and transient inactivation of EIF5A could prevent the inflammatory effects of the pathway without triggering widespread apoptosis.

According to Dondero, Senesco owns patents on the use of the siRNA constructs described in the study. He said the company is seeking to partner or out-license a pancreas-specific formulation of the EIF5A siRNA that is in preclinical development for diabetes.

Osherovich, L. *SciBX* 3(23); doi:10.1038/scibx.2010.692

Published online June 10, 2010

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