Moving upstream of diabetes

By Lev Osherovich, Senior Writer

There is a growing consensus in the medical community that early intervention is essential for treating diabetes.[1] However, there are no approved treatments for metabolic syndrome, a complex set of conditions that often precedes diabetes. Now, two papers[2,3] in the *Proceedings of the National Academy of Sciences* point to a trio of targets for treating obesity and insulin resistance, two key features of metabolic syndrome.

The studies suggest that targeting growth differentiation factor-3 (GDF-3) could reduce obesity, hitting activin B could boost insulin secretion and inhibiting the transforming growth factor-β receptor (TGF-β receptor) activin receptor–like kinase-7 (ALK-7) could do both—GDF-3 and activin B are both ALK-7 ligands.

Industry and academic researchers told *SciBX* that targeting this group of proteins is a new angle of attack for metabolic syndrome, but they added that the question of which of the targets to hit will require further preclinical study.

Acceleron Pharma Inc. has licensed the discoveries and already has ALK-7 derivatives in preclinical development.

The papers are both from a group led by Carlos Ibañez, professor of neuroscience at the **Karolinska Institute**.

In one study, Ibañez's team examined how knocking out ALK-7 and its ligands affected insulin secretion in the pancreas. "We have found a new mechanism to control insulin release by β-cells," Ibañez told *SciBX*. The ALK-7 circuit acts "to control the amount of insulin released in response to glucose," he added.

The second study focused on the metabolic functions of GDF-3, an alternative ALK-7 ligand that is secreted by adipocytes. Here, Ibañez's team discovered a separate role for ALK-7 in regulating obesity.

"This is the first clear-cut demonstration of the normal physiological role of GDF-3 in regulating metabolism," said Se-Jin Lee, professor of molecular biology and genetics at **Johns Hopkins University**.

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>
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Fat liver, skinny mouse

ALK-7 is a membrane-bound receptor for several TGF-β homologs that are involved in developmental patterning and cell growth.[4] Ibañez said his team found that despite developing normally, ALK-7 knockouts had higher serum insulin levels than wild-type controls. The mutant mice also developed enlarged β-islet cells and fatty livers.

Ibañez told *SciBX* that knocking out ALK-7 created a distinct form of insulin misregulation. "These mice are not diabetic, in that they still have normal glucose" when they are young, he said. "Young mice have high insulin in the blood, but are not insulin resistant."

However, the mice developed insulin resistance as they got older. Ibañez thinks this resulted from compensation in glucose sensing after a lifetime of high insulin.

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To determine how ALK-7 regulates insulin production, the researchers tested the effect of various ALK-7 ligands on insulin secretion in isolated pancreatic β-islet cells. The team found that knocking out activin B recapitulated the increased insulin secretion found in ALK-7 knockouts, thus suggesting that activin B inhibits insulin production by binding to ALK-7.

The second paper shows that ALK-7 wears a second hat as a regulator of fat deposition. When fed a high-fat diet, ALK-7 knockouts did not gain as much weight as wild-type controls did despite comparable food intake.

To uncover how ALK-7 controlled fat, Ibañez turned to GDF-3, which previous studies had implicated in fat accumulation in adipocytes.[5] Just like ALK-7 knockouts, GDF-3 knockouts proved resistant to weight gain induced by a high-fat diet compared with wild-type controls, suggesting that the receptor and ligand work together in adipose tissue.

Consistent with this idea, Ibañez's team found that ALK-7 was expressed in adipocytes and could be activated by GDF-3.

Together the studies show that activin B and GDF-3 control distinct functions of ALK-7. Indeed, overfed ALK-7 knockouts were lean but had high insulin levels, whereas overfed GDF-3 knockouts were lean despite normal insulin levels. Ibañez told *SciBX* that ongoing experiments are testing whether activin B knockouts, which have high insulin levels, are fat or lean when on a high-fat diet.

Angles of approach

Several therapeutic approaches for treating metabolic syndrome or diabetes could emerge from the *PNAS* papers. However, questions remain about which of the targets to hit and whether it is better to increase insulin secretion, reduce fat deposition or do both.

According to Jasbir Seehra, CSO of Acceleron, the ALK-7 system presents multiple targets, each with its own advantages and drawbacks.

At first blush, the clear target would be ALK-7 because blocking the receptor both reduces obesity and increases insulin. However, Seehra cautioned that ALK-7 may have other ligands with important functions, and thus knocking down the receptor may have side effects.

For treating obesity alone, Seehra thinks that inhibiting "ALK-7 will be powerful but not so selective," whereas inhibiting GDF-3 "may provide the desired effect."

Ibañez agreed and told *SciBX* that for obesity, "GDF-3 would be a good target, but we don't know as much about it" as other TGF-β proteins.

Targeting activin B could control glucose levels in patients with metabolic syndrome, and this approach is under consideration at Acceleron, according to Seehra.

Acceleron makes soluble fragments of TGF-β receptors to treat a range of diseases. The company's lead compound, ACE-011, a fusion protein combining the activin-binding portion of activin receptor type 2a with soluble IgG, is in Phase Ib trials for osteoporosis. The compound is partnered with **Celgene Corp.**

Seehra told *SciBX* that Acceleron is developing a soluble fragment of ALK-7 called ACE-06X and is optimizing the compound's binding affinity for GDF-3 using protein engineering.

In support of this approach, Ibañez pointed out that unlike ALK-7 knockout mice, the activin B knockouts produced excess insulin but did not develop insulin resistance late in life.

It is possible that the ALK-7 system's true calling is in treating full-blown type 2 diabetes. At least six approved diabetes drugs control glucose levels by stimulating insulin secretion in β-cells.[6]

Francine Gregoire, associate director of *in vivo* pharmacology at **Metabolex Inc.**, told *SciBX* that inhibiting the activin B branch of ALK-7 activity could be a good approach to "improvement of islet health and enhancement of β-cell mass."

In March, Metabolex started a Phase I trial of MBX-2982, an agonist of a β-cell receptor called G protein–coupled receptor 119 (GPR119), to treat type 2 diabetes. Activation of GPR119 stimulates the secretion of insulin by β-cells.[7]

At the end of the day, both Seehra and Ibañez agree that the specific approach will depend on the indication.

"It may be that you have to inhibit the receptor in certain diseases and the ligands in others," said Seehra.

Next steps

The biggest question is whether targeting the ALK-7 system can affect insulin levels or obesity in genetically normal adult animals. TGF-β proteins are best known as embryonic morphogens, and some researchers cautioned that some of the observed phenotypes in the two studies may result from developmental effects.

According to Seehra and Lee, the proof of therapeutic utility will be to administer antibodies against the three targets to adult mice and then monitor insulin and fat levels.

Moreover, the specific tissues in which these proteins act are not yet certain.

"We don't know which site of expression is responsible for the effects" of ALK-7, Ibañez said. "It's placed in a lot of tissues that could have an impact."

Ibañez plans to develop β-islet cell–specific knockouts to test whether ALK-7, activin B and GDF-3 act locally. An alternative mechanism might be that these proteins affect metabolism through the nervous system, like the appetite-regulating hormones leptin and ghrelin.

Gregoire agreed with Ibañez's plan, noting that potential "metabolic perturbations in other tissues" resulting from ALK-7 inactivation need to be explored "with tissue-selective knockout models."

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COMPANIES AND INSTITUTIONS MENTIONED

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