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ALK7's obese functions

By Chris Cain, Associate Editor

Reduced β-adrenergic signaling has long been associated with obesity, but the likelihood of triggering cardiovascular side effects has prevented companies from targeting the pathway for weight control. Now, a new—and possibly safer—way to upregulate β-adrenergic activity without using catecholamines has emerged from findings that show inhibition of ALK7 restores β-adrenergic signaling specifically in fat cells and decreases weight gain in mouse models of obesity.[1]

Acceleron Pharma Inc. has licensed the findings and is pursuing a discovery program for ALK7 (activin A receptor type 1C; ACVR1C) antagonists. ALK7 is a receptor in the transforming growth factor-β (TGFB; TGFβ) super family.

According to Carlos Ibanez, principal investigator on the study, the results are exciting because they suggest a way to combat obesity by making adipocytes more efficient rather than relying on dietary changes.

"Many current antiobesity approaches are directed toward decreasing appetite or intestinal absorption of nutrients. Here we are attempting to use endogenous mechanisms to increase metabolic rate by letting adipose tissue dispose of fat even in a situation in which it would otherwise be programmed to accumulate it," he told *SciBX*.

Ibanez is a professor of physiology at the **National University of Singapore** and professor of molecular neurobiology in the Department of Neuroscience at the **Karolinska Institute**.

Catecholamines such as adrenaline normally drive the breakdown and oxidation of lipids in adipose tissue. In obesity, insensitivity to catecholamines leads to various effects, including a reduction in lipolysis, with consequent weight gain.

However, systemic dosing of β-adrenergic agonists is not a viable strategy because they would trigger cardiovascular side effects. In addition, it has been difficult to develop obesity therapies that target catecholamine resistance because—other than the involvement of inflammation—very little is known about the mechanism linking the catecholamine pathway to the disease.[2]

Now Ibanez's team has discovered that ALK7 lies behind catecholamine resistance in obesity and that it limits adrenergic receptor-β (ADRB) expression and signaling in adipocytes under high-fat diet conditions.

In 2008, Ibanez's group showed that mice lacking *Alk7* accumulated less fat than wild-type mice, but there were no chemical probes available to test whether acute ALK7 inhibition could reproduce the effect.[3,4]

To dissect the mechanism, the team generated mice lacking *Alk7* expression specifically in adipose tissue. When fed a high-fat diet, the mice accumulated less fat, gained less weight and had less inflammation in adipose tissue than control mice with normal *Alk7* expression.

Acceleron founder and CEO John Knopf said that this experiment was key for pinning down the peripheral effect of ALK7 action. "The expression was known to be high in fat, but the knockout experiments were global, and you never quite know if the effect is secondary to other tissues. Here it is important they show that it is an intrinsic fat cell event."

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>
> ***—Carlos Ibanez, National University of Singapore***

Next, the Ibanez group took a closer look at the physiology of fat cells in the *Alk7*-deficient mice on a high-fat diet to find out whether the effects were caused by lower intake or greater burning of calories. The team found data supporting the latter. Adipocytes lacking *Alk7* showed increased energy expenditure and oxygen consumption compared with adipocytes from wild-type mice.

After ruling out that this increase in energy expenditure could be caused by the browning of adipose tissue, the team looked for other mechanisms that could be at work.

Because the increased energy expenditure was similar to that seen in mice treated with β-adrenergic agonists, the team tested whether *Alk7* deletion altered levels of β-adrenergic receptors. Indeed, levels of multiple ADRBs and their target genes were greater in mice with *Alk7* deletion that were on a high-fat diet than those in wild-type controls. The same was true in cultured *Alk7*-deficient human adipocytes.

Finally, the group wanted to determine the therapeutic potential of inhibiting ALK7. Because no antagonists of the receptor are available, the team used a chemical genetic approach pioneered by Kevan Shokat at the **University of California, San Francisco**. Shokat has developed knock-in mice in which individual kinases are engineered with a modified ATP-binding pocket, rendering them sensitive to inhibition by a synthetic analog of ATP. Shokat is professor and chair of the department of cellular and molecular pharmacology at UCSF.

Ibanez's group created knock-in mice that expressed an ATP analog–sensitive version of Alk7. An ATP competitive inhibitor decreased weight gain in mice on a high-fat diet compared with untreated controls or wild-type mice.

Results were published in *eLife*.

Accessing ALK

The next step for the researchers, according to Ibanez, is to develop ALK7 inhibitors and test them in animal models of obesity.

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Ibanez said that the preliminary safety data from *Alk7* knockouts look promising. In addition, because it is not widely expressed, it could provide a better safety profile than using β-adrenergic agonists.

"Blocking ALK7 enhances β-adrenergic signaling selectively in adipose tissue by preventing adipocyte resistance to catecholamines during nutrient overload. Because ALK7 is not expressed in heart, liver or muscle, targeting ALK7 could prove to be quite safe as it relies on endogenous levels of catecholamines," he said.

Alan Saltiel, director of the Life Sciences Institute at the **University of Michigan**, added that being able to target energy expenditure is a potentially promising approach but cautioned that it is still being validated in the clinic. "Obesity basically has two components: increased appetite and decreased energy expenditure. Based on the data presented here, inhibiting ALK7 will target the second problem," he said. "There are several clinical trials under way to attempt increasing energy expenditure, but no one really knows what can be achieved by this approach."

The most advanced program in the clinic that could increase energy expenditure by targeting peripheral sites is **Zafgen Inc.**'s beloranib, an inhibitor of methionine aminopeptidase 2 (MetAP2). The compound is in Phase III testing to treat obesity in patients with Prader-Willi syndrome, a rare genetic disorder that causes binge eating.

Saltiel added that because ALK7 is probably involved in other physiological processes, finding specific inhibitors that do not have side effects could be a "tall order." ALK7 is known to play roles in development, including in the CNS, and is expressed in adult neurons.

Knopf said that Acceleron licensed fundamental patents covering Ibanez's work in 2004, and the company has also filed its own IP covering ALK7 inhibitors.

Ibanez said that his team is focused on research on the function of ALK7 in human adipocytes and in other tissues in which it is expressed and is working independently of Acceleron. He added that the next challenge is to test whether inhibiting ALK7 can induce weight loss in an obese animal in addition to preventing weight gain.

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   Contact: Carlos F. Ibanez, Karolinska Institute, Stockholm, Sweden e-mail: carlos.ibanez@ki.se
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COMPANIES AND INSTITUTIONS MENTIONED

Acceleron Pharma Inc. (NASDAQ:XLRN), Cambridge, Mass.
Karolinska Institute, Stockholm, Sweden
National University of Singapore, Singapore
University of California, San Francisco, Calif.
University of Michigan, Ann Arbor, Mich.
Zafgen Inc. (NASDAQ:ZFGN), Cambridge, Mass.

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