Resistin becomes less futile

By Steve Edelson, Executive Editor

University of Pennsylvania researchers have removed a roadblock to studying the role of resistin in diabetes by developing a mouse model that has human-like expression of the target. Although the model may become a tool to study how the adipokine participates in the development of type 2 diabetes, it isn't clear if it will rekindle enthusiasm for resistin itself as a drug target.

When resistin was discovered in 2001, it seemed like a slam-dunk diabetes target—the adipokine was produced in rodent fat cells, circulated in the blood and contributed to insulin resistance.[1] But seven years later, no company has a disclosed resistin therapeutic in development.

A key holdup has been the fact that, unlike mice, humans express resistin in macrophages and not in fat cells, thus raising the question of whether the rodent observations would carry over to humans.

Now, the group that discovered resistin has moved a step closer toward providing an answer: its new mouse model expresses resistin only in macrophages.[2]

"The wrinkle came shortly after we discovered resistin, when we figured out that in humans it's not made in adipocytes, but rather in macrophages," said Mitchell Lazar, chief of the Division of Endocrinology, Diabetes and Metabolism at UPenn. "Initially that led to skepticism about whether the resistin findings in rodents would translate into man."

Further clouding the target's validity were genetics studies that "were all over the map," according to Lazar. "About two-thirds found a correlation between blood levels of resistin and obesity, diabetes and sometimes cardiovascular disease. But the other third of the time, if not more, there wasn't a difference."

He concluded that all the studies were small and "the assays were not good."

Larger population-based studies have found that higher levels of resistin and polymorphisms in the gene for resistin are associated with metabolic syndrome and diabetes.[3,4] But the questions of how—and if—macrophage-produced resistin plays a role in diabetes still remained.

To answer the question, a group at UPenn and the **University of Oxford** took a resistin knockout mouse model and engineered the mice to produce human resistin in macrophages. The results were published in the *Journal of Clinical Investigation*.

"The mice were indistinguishable from normal until we put them on a high-fat diet," said Lazar. At that point, the mice "recapitulated the human condition—they get fat, gain weight and become diabetic."

A known part of that process is macrophage infiltration of adipose tissue.[5,6] However, Lazar said, the researchers found that if the mice make resistin, "the macrophages infiltrate earlier and speed up and exacerbate the insulin resistance."

Indeed, the authors of the *JCI* paper concluded that "macrophage-derived human resistin is capable of exacerbating the pathophysiological consequences of obesity," specifically progression to type 2 diabetes.

Model (or) target

Although the *JCI* paper lays to rest the question of whether human resistin is involved in diabetes, it remains unclear whether the target is a good intervention point. For example, its receptor is unknown, and blocking resistin would have to occur in multiple tissue types.

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> *—David Karpf, Metabolex Inc.*

The good news is that the new mouse model "provides a preclinical way to test the concept that interfering with resistin will improve insulin resistance and diabetes," said Lazar.

David Karpf, CMO of diabetes company **Metabolex Inc.**, agreed. "This work provides a valid animal model for testing drugs," he said.

Karpf was less optimistic that anti-resistin therapeutics would make good drugs. "I see resistin as a player, but I don't see it as the lynchpin" in the development of diabetes, he said.

Karpf also noted that results in the *JCI* paper showed that resistin knockout mice also gained weight and became insulin resistant when fed a high-fat diet.

"This process was just augmented in the presence of resistin," he told *SciBX*. "It may well play an accommodating role and ramp up to the generalized inflammatory stage, but the data don't suggest that taking resistin out of the picture would prevent the disease in the presence of adiposity."

Lazar agreed that the feedback loops in the immune system that lead to an inflammatory state are abundant. "If you take out one part, you're not going to knock out the whole process," he said.

Because of the redundant etiology of insulin resistance, Karpf said he's not sure the results reported in *JCI* would renew enthusiasm among any companies that had dropped resistin as a drug target. "Instead," he said, "it's an important paper for understanding, on a detailed molecular level, the pathophysiology of what we're seeing" as insulin resistance develops.

Metabolex and partner **Johnson & Johnson** are developing MBX-102, a selective peroxisome proliferation activated receptor-γ (PPARG; PPAR-γ) modulator that is in Phase II/III testing to treat type 2 diabetes.

Any antiresistin therapeutic would likely involve physically neutral-

izing the molecule itself, such as with an antibody or antisense. That will be tricky, said Lazar, because "you'd have to neutralize resistin in both the bloodstream and in adipose tissue."

If a company did pick up resistin as a drug target, it would also have to proceed without knowing the identity of resistin's receptor.

"We've tried to find the resistin receptor but haven't been able to do it for technical reasons," said Lazar. "It might not have a classical receptor. If a pharmaceutical company were to find it, they'd have a terrific leg up on everyone."

Lazar said he is in talks with undisclosed companies about licensing the resistin discoveries.

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COMPANIES AND INSTITUTIONS MENTIONED

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