An obesity angle for GPR120

By Kai-Jye Lou, Staff Writer

An international team of researchers has shown that dysfunction of the fatty acid receptor GPR120 leads to obesity and obesity-associated metabolic disorders such as glucose intolerance and fatty liver.¹ The findings come less than two years after another team had reignited interest in GPR120 as a diabetes target.

G protein-coupled receptor 120 (O3FAR1; GPR120) was identified as a target for both diseases in late 2004 after a group in Japan reported that the receptor triggered the release of glucagon-like peptide-1 (GLP-1) from intestinal cells when stimulated by unsaturated long-chain free fatty acids.² GLP-1 decreases food intake and stimulates insulin secretion.

However, GPR120 fell out of favor as a therapeutic target because little else was known about the receptor's physiological function and follow-up work by companies suggested its direct effect on GLP-1 release would be minor at best.³

In 2010, researchers at the **University of California, San Diego** showed that GPR120 signaling also was important for the anti-inflammatory and insulin-sensitizing effect of ω -3 fatty acids—the active ingredient in **GlaxoSmithKline plc's** lipid-lowering drug Lovaza.⁴

Now, **Kyoto University** and a consortium of European research institutes and universities have reported that in mice fed a high-fat diet, *Gpr120* deficiency led to greater susceptibility to obesity and more severe glucose intolerance, insulin resistance and fatty liver than wild-type *Gpr120* expression.

In the *Gpr120*-deficient mice, the group also found dysregulated lipogenesis and decreased production of C16:ln7-palmitoleate, an adipose tissue-derived lipid hormone that stimulates muscle insulin action and suppresses fatty liver.⁵

The Kyoto group was led by Gozoh Tsujimoto, a professor in the Department of Genomic Drug Discovery Science who also was corresponding author on the 2004 paper.

The team in Europe, led by Philippe Froguel, chair of genomic medicine in the School of Public Health at **Imperial College London**, carried out genetic association studies to identify links between *GPR120* and obesity.

"The hypothesis was that if *GPR120* and dietary ω -3 fatty acids are so important to human metabolism, mutations that impair the activity

of these fatty acids on the receptor should be associated with disease," said Froguel.

In a cohort of 6,942 obese individuals and 7,654 control subjects of European descent, a missense mutation in *GPR120* that inhibited its signaling was significantly associated with obesity ($p=8\times 10^{-6}$).

Data were published in *Nature*.

"Our current work confirms GPR120's role as a lipid sensor and also shows that the receptor regulates whole-body lipid metabolism, especially fat distribution," said Tsujimoto. "Our findings give additional evidence that supplementation with GPR120 agonists or developing strategies that normalize GPR120 function could help treat pathological obesity. The data also suggest that we can adopt a preventative strategy where we identify and stratify out individuals susceptible to pathological obesity and get them to reduce their fat intake."

Froguel agreed. "The work suggests that even if you have a genetic defect in ω -3 signaling, nothing bad happens as long as you eat a healthy diet," he told *SciBX*. Indeed, the researchers found that *Gpr120*-deficient mice and wild-type mice fed normal diets had comparable body weights.

Froguel added that the findings also partially explain how ω -3 fatty acids affect metabolism and why they probably have beneficial effects.

"The results in this publication firm up the relationship between GPR120 and metabolic disorders including obesity," said Brian Lavan, senior director in biology at **Metabolex Inc.** "The

most interesting finding to me was showing the relationship between the GPR120 deficiency and the production of C16:ln7-palmitoleate because it points to a possible role of GPR120 in modulating the production of lipokines. Clearly, if the receptor is able to do so, this would be a new area of GPR120 biology that's worth exploring."

Mechanism and regulation

The next step is conducting studies that clearly determine how GPR120 activity is regulated and whether activating the receptor will have a therapeutic effect in obesity.

"The current study didn't really explore the mechanisms that underlie the observed effects of *GPR120* deficiency on metabolism and raises interesting questions about the receptor's biology, for which we don't yet have answers," said Lavan. "The key question that needs to be addressed in future studies is whether activation of this receptor is going to produce a benefit in a broad population of patients with obesity and/or type 2 diabetes."

Gary Schwartz, a professor in the Department of Medicine and the Department of Neuroscience at the **Albert Einstein College of Medicine of Yeshiva University**, added that it will be important to profile the tissue distribution of GPR120 and to carry out studies to understand how the receptor itself is being regulated at the whole-body level and in individual tissues as a function of refeeding after a fast.

"The researchers will also need to prioritize future studies to explore how this receptor is regulated by the body during normal physiological

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—Gozoh Tsujimoto,
Kyoto University

feeding and fasting states and in mammalian models of diet-induced obesity and type 2 diabetes,” he told *SciBX*.

Tsujimoto said his group is now working to determine why obese individuals with a deficiency in GPR120 are far more susceptible to obesity-associated metabolic disorders than obese individuals without the deficiency.

“It will also be important to determine whether bypassing GPR120, for example, by activating distal targets in the receptor’s signaling pathway, could potentially be helpful for treating obese patients that express the GPR120 defect,” he added.

Froguel said the European group is trying to find better phenotype carriers of the identified *GPR120* mutation and is taking a closer look at the carriers’ appetite and metabolism. “We are also looking more carefully at the effect of the gene on diabetes risk and looking for other sensors of diet that could be obesity genes,” he told *SciBX*.

Genomic drug discovery company **Pharma Frontier Co. Ltd.**, which was cofounded by Tsujimoto, has filed multiple patent applications covering GPR120 agonists and compounds that act on the GPR120 signaling pathway. The work is available for licensing. The company was not involved in the current study.

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