FEATURE

Key Advances in Understanding the Pathogenesis of Diabetes

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Domenico Accili, MD, Columbia University, New York, New York, USA, delivered the Claude Bernard Lecture, reviewing key advances that have increased our understanding of the pathogenesis of diabetes.

According to Dr Accili, in the 1980s diabetes researchers thought that the disease could be conquered if the paramount issues in its pathogenesis could be determined—in particular,

- Why does glucose fail to promote glucose uptake?
- Can a more durable insulin secretagogue be developed?

Research consequently focused on developing tracer methods to evaluate glucose disposal and how insulin functioned to promote glucose uptake. Although it was thought that the subsequent cloning of numerous glucose transporters would provide clarification on these matters, decades later they remain unresolved. In fact, there has been a shift in focus.

Dr Accili discussed research performed in his laboratory in 1995 in which blocking the ability of insulin to promote glucose disposal in fat and muscle did not cause β-cell stress and hyperglycemia. This research led him to hypothesize that it was essential to focus on other sources of insulin resistance.

In what he refers to as "the new biology of diabetes," Dr Accili discussed the key pathophysiologic abnormalities involved in the progression of type 2 diabetes mellitus (T2DM), which are now known to include the following:

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- Abnormal hepatic lipid synthesis and lipoprotein production
- Altered endothelial response to vasoactive stressors
- Alterations in adipostatic hormones
- Numerous inflammatory changes
- Possible central nervous system involvement
- Cellular biological changes that destroy pancreatic β cells

Dr Accili emphasized that understanding this complex set of interactions has tremendous potential for the development of novel therapies.

In the 1990s, a new protein, the FoxO (forkhead box O) transcription factor, was discovered to play a central role in hepatic gluconeogenesis—one of the unsolved mysteries of diabetes. Of the many proteins in this family of transcription factors, FoxO1 is particularly important in the control of insulin-regulated gluconeogenesis in the liver through the enzyme glucose-6-phosphatase (G6Pase). G6Pase is required to allow the liver to release glucose. It is induced by glucagon during fasting and suppressed by insulin after a meal. If one genetically removes FoxO, Dr Accili noted, G6Pase is no longer induced by fasting nor suppressed by insulin. Moreover, if one blocks the ability of insulin to inhibit FoxO, the effect of insulin on G6Pase is also blocked—indicating that it requires FoxO inactivation. FoxO therefore oversees the conversion of G6Pase to glucose that is necessary for hepatic glucose conversion, and insulin suppresses this step through FoxO. This discovery represents important progress, even though it has not resulted in complete understanding of how insulin controls hepatic glucose production (HGP).

Since its discovery, FoxO has continued to be useful in furthering understanding of insulin action. Research has now shown that through FoxO, insulin also has roles in the following:

- Appetite control
- Energy efficiency
- Hepatic glucose and lipid metabolism
- Differentiation of endocrine progenitor cells
- β-cell function at various levels
- Endothelial response to atherogenic processes

Dr Accili reviewed 2 areas of research with important implications for clinical decision making, highlighting the potential for them to give rise to new diabetes therapies.

DIABETES AND ATHEROSCLEROSIS

Statistics published by the American Heart Association have shown that heart disease and stroke are the major causes of death among patients with diabetes. A growing emphasis on helping patients achieve tight glycemic control has reduced the risk of microvascular complications associated with diabetes, but it remains a challenge to reduce the risk of macrovascular complications, which account for half of all diabetes-related health care costs. The liver is a key contributor to the atherogenic process, primarily because of the release of atherogenic lipoproteins.

Insulin affects hepatic lipid metabolism and may promote an atherogenic profile, Dr Accili noted. While FoxO is important in the control of glucose production through its regulation of G6Pase, FoxO also regulates its opposing enzyme, glucokinase (GCK). Under normal physiologic conditions, as glucose flows in and out of the liver, plasma glucose levels are maintained within a narrow range by the interplay of the GCK:G6Pase ratio. GCK also has the ability to promote lipogenesis. In the absence of FoxO, neither of these mechanisms functions appropriately. Consequently, instead of glucose being released by the liver for use by other tissues as an energy source, it is converted into fat. Additional experimental work has also confirmed the strong relationship between GCK levels and the amount of triglycerides in the liver [Peter A et al. *J Clin Endocrinol Metab*. 2011].

Dr Accili explained that the intertwined nature of these processes has numerous implications. In patients with insulin resistance, as insulin levels increase to suppress HGP, they also promote GCK-dependent hepatic fat accumulation and triglyceride synthesis. Consequently, he proposed that an atherogenic lipoprotein profile is the price paid by the body to suppress HGP in the early stages of diabetes. He stressed that, at the clinical level, prevention of cardiovascular disease in T2DM must begin early, possibly even before the onset of fasting hyperglycemia. Trying to design a hepatic insulin sensitizer devoid of effects on lipoproteins will prove challenging.

WHY β CELLS FAIL

The intrinsic susceptibility for the functional exhaustion of β cells differentiates individuals who go on to develop T2DM from those who do not. Although insulin resistance has been considered to be pivotal in the development of T2DM in recent decades, it does not lead to T2DM unless there is also β-cell dysfunction, because healthy β cells can compensate for insulin resistance by increasing their number and the production of insulin [Kitamura T. *Nat Rev Endocrinol*. 2013]. β-cell failure is initially reversible, however, even after the onset of hyperglycemia. Dr Accili went on to emphasize 3 key islet abnormalities in T2DM:

- An impaired insulin response to a stimulus
- Reduced β-cell mass
- An inappropriate glucagon response

Dr Accili discussed the changes in FoxO1 activity in the β cell during the progression of diabetes, noting that, in early diabetes, FoxO1 is activated by moving into the nucleus, while in advanced stages of the disease, FoxO1 disappears from the β cell along with insulin. Research has also now shown that dedifferentiation, not cell death, is the main cause of β-cell failure in diabetes and that dedifferentiated β cells convert to non-β endocrine cells. FoxO1 is implicated in these mechanisms [Talchai C et al. *Cell*. 2012]. According to Dr Accili, hyperglycemia-induced loss of FoxO1 alters β-cell metabolic flexibility, and this metabolic inflexibility sets the stage for β-cell failure. He noted that, since data from a recently completed study [Kim-Muller JY et al. *Cell Metab*. 2014] have also demonstrated the occurrence of β-cell dedifferentiation in people with T2DM, the paradigm for new therapeutic approaches to T2DM should shift to one that aims to restore β-cell differentiation.

In his concluding remarks, Dr Accili described another interesting discovery from his laboratory—namely, that genetic removal of FoxO1 from endocrine progenitor cells in the gastrointestinal tract converts these gut cells into functional insulin-producing cells. Although this was initially seen in mice [Talchai C et al. *Nat Genet*. 2012], more recent work also demonstrated this mechanism in genetically engineered human cells [Bouchi R et al. *Nat Commun*. 2014]. Dr Accili added that, in addition to producing insulin, these cells release insulin in a physiologic-like manner. These findings highlight the potential to design drugs that can convert cells in the gut into insulin-producing cells, as a way to treat type 1 diabetes and possibly even T2DM.