# Cell-signaling pathway has key role in development of gestational diabetes

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Researchers at the University of Pittsburgh School of Medicine have identified a cell-signaling pathway that plays a key role in increasing insulin secretion during pregnancy and, when blocked, leads to the development of gestational diabetes. Their findings are available online today in *Diabetes*, one of the journals of the American Diabetes Association.

During pregnancy, pancreatic beta cells should expand and produce more insulin to adapt to the needs of the growing baby, explained senior investigator Adolfo Garcia-Ocana, Ph.D., associate professor of medicine, Division of Endocrinology and Metabolism, Pitt School of Medicine. Newborns can suffer complications if the mother's blood glucose is abnormally high during pregnancy, a condition known as gestational diabetes.

"Not much was known about the maternal mechanisms that lead to increased beta cell number and function during pregnancy," Dr. Garcia-Ocana said. "But research has shown that high blood glucose in pregnancy can have long-term health consequences for the child, as well as a greater risk of hypertension, type 2 diabetes, and high cholesterol for the mother."

His team began studying a protein called hepatocyte growth factor (HGF), which was discovered by George K. Michalopoulos, M.D., Ph.D., professor and chair, Department of Pathology, Pitt School of Medicine, in 1990. Blood levels of HGF are markedly increased in pregnancy. The protein interacts with a cell surface receptor called c-MET.

The researchers engineered mice that lacked the c-MET receptor in pancreatic cells and found that their beta cells functioned correctly, keeping blood glucose within normal parameters in adult mice. But when the mice got pregnant, they took on the features of gestational diabetes.

"Mice that didn't have the c-MET receptor in their pancreas had lower plasma insulin levels, higher blood glucose and impaired ability to regulate glucose levels," Dr. Garcia-Ocana said. "Without the receptor, they couldn't respond to HGF." Also, unlike normal healthy pregnant females, these mice didn't produce more beta cells, had more beta cell death and so had reduced beta cell mass.

"These findings provide the first direct evidence that HGF/C-MET signaling pathway has an important role in maternal beta cell adaptation during pregnancy," Dr. Garcia-Ocana noted. "Perhaps women who have a variation in the HGF gene or in the c-MET receptor are predisposed to developing gestational diabetes because they cannot adequately compensate for the increased insulin demands of pregnancy."

In future work, he and his team will explore HGF signaling in pregnant women, which could one day provide a new means of diagnosing, treating or preventing gestational diabetes.

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