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Team reveals molecular mechanism underlying a form of diabetes

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By investigating a rare and severe form of diabetes in children, University of Iowa researchers have discovered a new molecular mechanism that regulates specialized pancreatic cells and insulin secretion. The mechanism involves a protein called ankyrin, which UI researchers previously linked to potentially fatal human heart arrhythmias.

The findings, which appear this week in the Early Edition of the Proceedings of the National Academy of Sciences, may help identify new molecular targets for treating both rare and common forms of diabetes and hyperinsulinemia.

The Centers for Disease Control and Prevention estimates that 23.6 million people have diabetes in the United States. The condition doubles the risk of death and includes complications such as heart disease, stroke, eye and kidney problems, and peripheral vascular disease.

The University of Iowa team, working with researchers at Washington University in St. Louis, used animal and cellular models to focus on a gene mutation linked with permanent neonatal diabetes mellitus. Children with this genetic form of diabetes have symptoms by age 6 months and require lifelong dependence on insulin to maintain proper glucose levels.

The team discovered that the specific human gene mutation disrupts the ability of the protein ankyrin to regulate a key protein complex known as

the KATP channel.

"We have known for some time that human mutations in the KATP channel complex may cause diabetes or hyperinsulinemia," said Faith Kline, Ph.D., the study's lead author and postdoctoral fellow in internal medicine in the University of Iowa Carver College of Medicine. "Now we know something about how this specific KATP channel mutation results in disease.

"The KATP channel essentially functions as a gatekeeper for insulin secretion by pancreatic beta cells. Without proper regulation by this gatekeeper, the pancreatic beta cells are unable to efficiently regulate insulin secretion."

In a healthy individual, pancreatic beta cells respond to changes in blood glucose levels by secreting the appropriate amount of insulin. Beta cell dysfunction may result in abnormal blood glucose regulation and severe diabetes.

"A key finding in this study was identifying the ankyrin protein in the pancreatic beta cell, which is a type of excitable cell. Ankyrins also play critical roles for ion channel regulation in other excitable cells, such as neurons and heart cells called cardiomyocytes," said the paper's senior author, Peter Mohler, Ph.D., University of Iowa associate professor of internal medicine and a Pew Scholar.

Specifically, the team found that the gene mutation prevents most KATP channels from binding with ankyrin, which typically acts as a cellular chaperone. This failure prevents the KATP channels from reaching their normal destination in the cell membrane.

"Ankyrin proteins are like cellular taxi-cabs that carry passenger channels to the cell membrane. In the case of this KATP gene mutation,

the ankyrin and channels cannot interact properly, and so the channels basically 'miss their ride' and do not get to the desired location," Mohler said.

The team also found that the few mutant KATP channels that do reach the pancreatic cell membrane do not respond to alterations in cellular metabolism. As a result, the pancreatic beta cells do not release insulin appropriately.

"This is another exciting example of how understanding the basis of rare disease has provided unexpected and fascinating insight into the molecular pathways that govern human physiology," Mohler said.

Source: University of Iowa (news : web)