# Protein power: Researchers trigger insulin production in diabetic mice

January 8 2008

If the human body were a stage, then proteins would rank among the lead actors in the play we call “Life.”

These large biological molecules hold many starring roles, and their lines are dictated by information encoded in our genes. They are production powerhouses, regulating the basic processes of living and controlling countless functions. Many are enzymes that produce or use energy. Others regulate genes.

Researchers are increasingly studying proteins as potential therapies for a variety of dread diseases because they can influence cell behavior by fueling or dampening certain molecular signals.

Now University of Florida researchers have coaxed liver and pancreatic cells within diabetic mice into churning out insulin by injecting the animals with a naturally occurring protein called Pdx1, opening up a new research avenue that someday could lead to safer treatments for type 1 diabetes. Pdx1 activates the genes controlling the development of the pancreas cells that make and release insulin to maintain safe levels of glucose in the body. The UF research team’s novel approach is described online in the journal *Diabetes*.

“Pdx1 is so special because it possesses a unique amino acid sequence that acts as a sort of molecular passport, allowing it to pass freely into cells, enter the nucleus and activate insulin production and release,” said lead scientist Dr. Li-Jun Yang, an associate professor of pathology,

immunology and laboratory medicine at UF's College of Medicine.

Earlier research has shown that inserting the Pdx1 gene into liver or pancreas cells can induce insulin production, but most gene therapy methods use viruses to introduce a piece of genetically engineered DNA into cells. The disadvantage of such approaches is that researchers can never be certain the viruses are entirely harmless, Yang said.

The idea with protein therapy is that eventually a person's own cells could be reprogrammed to naturally produce the hormone, restoring the body's ability to properly regulate blood sugar levels without having to use a potentially hazardous virus to slip corrective genes into the body or having to transplant pancreatic cells from someone else. That could eliminate the adverse effects sometimes associated with gene therapy and eliminate the need for lifelong suppression of the immune system so transplanted cells are not rejected, Yang said.

"We sought to see what happens if we inject highly pure Pdx1 protein into (the abdomens of) diabetic animals," said Yang, who is also a founder and head of the scientific advisory board for Transgeneron Therapeutics Inc., which seeks to develop Pdx1 as a treatment for diabetes. UF holds a provisional patent on Pdx1 protein therapy. "Amazingly, the treated mice did all the rest. Upon daily injection of this protein for 10 days into diabetic animals, their blood glucose levels became normalized within two weeks following the first injection. We repeated the experiment six times, and we got the reproducible result every time. What is remarkable is that the protein also promotes regeneration of insulin-producing cells in the pancreas, allowing the diabetic mice to become normal."

Yang said there is now reason to believe normal blood sugar levels can be maintained for long periods, suggesting that an infrequent Pdx1 injection might someday replace daily insulin injections. Even more

importantly, the reprogrammed and regenerated cells should make and release insulin, automatically maintaining safe blood sugar levels, she said.

“Right now, promoting beta cell regeneration has become such a hot topic,” she added. “The trick is to figure out how to trigger glucose-regulated insulin-producing cells to regenerate.”

Still, the approach will have to be tested in studies that assess its safety before scientists could conduct patient trials to determine whether it works in people, studies that are still years away.

“What’s so innovative about UF’s approach is the ability to normalize blood glucose levels in diabetic mice simply by delivering Pdx1 protein in the target cells, thus effectively eliminating the side effects associated with gene therapy,” Yang said.

Dr. Joel Habener, a professor of medicine at Harvard Medical School whose research team was one of three groups that discovered Pdx1 and identified it as an important regulator of pancreas development, said using viruses as vectors for gene therapy in humans can pose problems because of the body’s immune reaction to them. He heralded the UF findings and said the idea of using a protein to correct a condition like diabetes is appealing because it is naturally occurring, “not a chemical compound that’s been synthesized from the mind of a chemist that’s a foreign substance.”

“What these findings teach is there is promise for a therapeutic approach to the treatment of diabetes,” he said. “I think one of the really major breakthroughs here is the demonstration of principle that the naked protein in and of itself can get into cells and cause changes that are remarkable in a mouse model of type 1 diabetes, the regeneration of the insulin-producing cells in the pancreas.”

Source: University of Florida