THE HARTWELL FOUNDATION

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Harnessing the Alpha-Cell for Diabetes Treatment

Diabetes is one of the most common chronic diseases in children. It is an increasingly prevalent disease affecting over 200,000 children in the U.S. There are two main forms of diabetes; both characterized by high blood sugar. Type 1 diabetes (T1D) is a chronic metabolic (autoimmune) disorder characterized by lack of insulin production in the pancreas. The more common Type 2 diabetes (T2D), is characterized by failure of the body to respond well to the presence of insulin and is most often associated with obesity. The presence of excess glucose in the blood can damage eyes, kidneys and nerves; trigger heart disease and stroke; and cause frequent infections and slow wound healing as a result of poor circulation in limbs so severe that in some cases, requires limb amputation. Unfortunately, while T1D and T2D are classically thought to be due to a deficiency in the action of insulin, a hormone secreted by pancreatic beta cells. However, insulin replacement fails as a cure for diabetes. In this regard, another key driver of disease pathology in T1D and T2D is thought to be played by a hormone called glucagon, which is secreted from pancreatic alpha cells when blood sugar levels are low, to signal the liver to discharge glucose into the blood. Glucagon also plays a major role in potentiating glucose-stimulated insulin secretion. Unfortunately, targeted inhibition of glucagon action as a therapy has also not been successful. Remarkably, bariatric surgery performed on the stomach or intestines to induce weight loss causes immediate and permanent remission of T2D (as well as a reduction in the severity of T1D symptoms) by improving blood glucose regulation. While the mechanism for the effect is unknown, apparently physical re-configuration of the tissues is sufficient to generate an adaptive response that alters favorably intestinal glucose metabolism and disposal. However, bariatric surgery is not practical as an intervention for diabetes, in part because it is not without risk. Ideally, a pharmaceutical strategy that recreates the effect of bariatric surgery to normalize blood glucose regulation would benefit the large number of children diagnosed with diabetes. To address this need, I propose to manipulate a novel biochemical pathway I discovered while using a mouse model of bariatric surgery; a pathway that appears to regulate pancreatic islet function. I hypothesize that identifying the factors that mediate the pathway will provide a way to turn off the glucagon signal for blood sugar regulation by shifting alpha-cells to produce an anti-diabetic hormone instead of glucagon. The effect should be to increase insulin secretion and expand beta-cell numbers. If I am successful in developing a targeted therapy to lower blood glucose by shifting the alpha-cells from being pro-diabetic to anti-diabetic, the result may mean a cure for diabetes.