A Story of Diabetes, Tuberculosis Vaccines, and How They May Live Happily Ever After

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Type 1 diabetes (T1D) is defined as the absolute loss of insulin producing beta-cells in the pancreas. To be clear, genetic predispositions and environmental triggers can cause this loss at any age. Without insulin, the body cannot move glucose across cell membranes from the blood and into tissues where cells must use it to generate energy. As a result, the body is starved while excess glucose builds up in the blood no-where to go. Without any insulin to utilize glucose, the cells in our bodies are forced to catabolize fats and proteins for energy while high glucose concentrations damage the endothelial linings of small capillaries such as those in the eyes, kidneys, reproductive organs, and periphery.

Knowing that most cases of T1D are the result of autoimmune dysfunction (which wipes out the insulin producing beta-cells), how have we tried curing T1D? To understand potential cures, we need to understand that it's the memory cells who recall and recognize beta-cell specific surface proteins. Upon recognition, they release antibodies that mark them for destruction. As a result, they cannot naturally regenerate to restore a prediabetic state.

So why not use stem cells to regenerate beta-cells? Regrettably, extracting bone marrow stem cells is deeply invasive, implants may cause cancer, and only a few months after implantation beta-cells are wiped out again. "While the early results were promising, with some 70% of the patients requiring no insulin injections after two years, at five years, most of these patients had deteriorated and required insulin supplements, despite some having received more than one transplant of islets (Lee, Gan, & Calne, 2012)."

Scientists are working on encapsulating these stem cells in semi permeable membranes so they're protected from the immune system, although research "has not yet been meaningfully translated into clinical islet transplantation (Krishnan et al., 2014)."

This is where the Bacillus Calmette-Guerin (BCG) vaccine comes in; a live attenuated tuberculosis (TB) vaccine employed worldwide since the early 1900s. Not only is it a cheap and

accessible vaccine, it has also been used as a "potential treatment for cancer (Wang & Lin, 2008)."

How has such a common vaccine managed to "significantly reduce the blood glucose levels," otherwise, the [1]HbA1c levels of diabetics (Faustman, 2017)?

The BCG vaccine is known to increase systemic levels of a cytokine, tumor necrosis factor (TNF) (Faustman, 2012). This cytokine can induce "significant changes in gene expression which ultimately help to increase regulatory T-cells while removing self-reactive memory cells," (Faustman, 2017) those which cause the autoimmune dysfunction. Regulatory T-cells tone down the immune response allowing beta-cells to regenerate, restoring insulin production. There have been promising results to support this hypothesis seen by the significant lowering of [1]HbA1c levels of diabetic trial subjects (Kühtreiber et al., 2018). However, after failing to show that beta-cells indeed could permanently be restored (Kühtreiber et al., 2018), a second hypothesis had to be adopted. If T1 diabetics did not continue producing insulin, how were their [1]HbA1c's being lowered?

It might simply be more glucose utilization around the body. BCG appeared to cause a "systemic shift in glucose utilization, shifting from primarily oxidative phosphorylation to aerobic glycolysis (Kühtreiber et al., 2018)." By putting the body in a higher state of glucose utilization, hyperglycemia could be better treated via an altered metabolic state. This change in metabolism may be related to the epigenetic changes that come with the vaccine. Certain genes were being upregulated (turned on) via demethylation of DNA, reprogramming cells to promote aerobic glycolysis (Kühtreiber et al., 2018). Whether this metabolomic shift takes place throughout the body or only in specific regions is yet to be understood.

Sometimes, science is a lot of shooting in the dark. Who knew that a TB vaccine could have potential significance for T1D treatment. Who knew that even frontline researchers can't figure out how the molecular biology comes together. Nevertheless, this is an area of work that can shine light on novel medical insights; this is how a TB vaccine and diabetes may live happily ever after.

Words: 666

[1]HbA1c: Glycalated hemoglobin is an index of long term (2-3 month) average blood glucose concentrations.

Citations

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