Regrowth of beta cells with small molecule therapy

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Background:

Type 1 diabetes (T1D) results when immune cells mistakenly destroy beta cells, a specialized cell in the body that produces insulin. Insulin is required for storing energy from the foods we eat, and so is essential for our normal bodily functions. Currently there is no cure for T1D and since people with T1D don't produce enough insulin they must receive insulin from other sources in order to live. The reasons why beta cells are destroyed in this disease are still a mystery. In this project, we found that a small subset of beta cells turned on a known growth pathway before the disease occurred in a mouse model. This led us to think that this pathway might be a way to compensate for beta cell loss by regrowing, or replenishing the pool of beta cells. We hoped to encourage this potential growth of beta cells in such a way that could reverse T1D and restore normal levels of insulin.

Results:

As we investigated the changes occurring in beta cells further, we found that rather than activating a growth response, these beta cells were adopting a growth arrested state called senescence. Thus our initial hypothesis was wrong. Even more remarkable, the senescent beta cells seemed to be promoting the progression of the disease, as they produced signals that encouraged further beta cell death and invasion by immune cells. We also found evidence that beta cells become senescent in humans with T1D and those at high risk for developing T1D by looking at markers for senescence in beta cells from human donors. In order to determine whether senescent beta cells were actually promoting the disease, we thought that if we could selectively kill this small subset of beta cells, it would spare the remaining majority of non-senescent, healthy beta cells. Using drugs that specifically kill off senescent cells, we found that treating our mouse model with these drugs prevented them from becoming diabetic. We also found that the drugs were in fact depleting senescent beta cells from these mice, but not killing off the immune cells.

Conclusions:

In conclusion, we have identified a new and important factor in the disease process in T1D, where some of the beta cells (the senescent ones) are actually contributing to the destruction process. This represents a radical change in the way T1D has been understood, where beta cells are just passive victims. We have also proved the concept of using drugs that selectively kill senescent cells as therapeutics for preventing T1D in our mouse model. Although it is unclear whether this approach would work in cases of established T1D, in the future, we envision that we may be able to prevent T1D in people and provide a therapeutic benefit for new T1D patients using a similar approach.

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