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Is It Possible to Regenerate Human Beta Cells?

Type 1 diabetes mellitus (T1DM) is an autoimmune disease where the body's own immune system mistakenly attacks and destroys the pancreatic beta cells, which are responsible for producing insulin. This process can begin long before the disease is diagnosed, sometimes months or even years in advance, and by the time it's finally detected, most of these cells have already been lost. Until recently, it was believed that the loss of these cells was irreversible. However, recent advances in research have reignited interest in the possibility of regenerating these cells as a potential strategy for treating this disease (1, 2).

In the early stages of type 1 diabetes mellitus (T1DM), beta cell destruction occurs progressively. However, recent studies have revealed that, even after years of disease, many individuals still retain a small number of functional beta cells. This finding opens up a hopeful possibility: if we can get these remaining beta cells to multiply, it might be possible to partially restore endogenous insulin production, thereby reducing the need for external injections. This strategy wouldn't only benefit people with T1DM. In T2DM although beta cell destruction isn't due to the immune system, these cells experience a process of exhaustion because of insulin resistance. Therefore, therapies aimed at **regenerating** beta cells could be beneficial for both forms of diabetes.

However, curing T1DM necessarily involves controlling the autoimmune attack that destroys beta cells. Today, treatments are being developed that aim to modulate the immune system to prevent or even reverse this damage. Some promising approaches include the use of regulatory T cells (lymphocytes), which could curb the immune cells' attack on the pancreas, and immunosuppressive treatments that prevent direct damage to beta cells (3, 4). Nevertheless, significant challenges remain. Thoroughly understanding the mechanisms that perpetuate autoimmunity in T1DM and finding ways to avoid severe side effects related to immunosuppression are problems that need to be solved.

But even if immunological damage is halted, this isn't enough to cure T1DM. Most people with T1DM suffer from an almost total loss of functional beta cells. Therefore, promoting the **regeneration or proliferation** of the remaining beta cells is essential for a complete cure. And here we encounter several challenges (1, 2). Human beta cells are highly specialized and differentiated, with a limited capacity to divide and proliferate in adulthood. Furthermore, when cultured in the lab, they tend to lose their ability to produce insulin or "dedifferentiate" into other cell types that are not functional. Added to this is the complexity of the molecular signals that regulate cell regeneration. It's not just about getting beta cells to divide; it's also necessary to ensure that these newly generated cells differentiate correctly and function properly. The **pancreatic microenvironment**, with specific signals that enable cell differentiation, plays a fundamental role in this process. Reproducing this complex network of signals under laboratory conditions has proven very difficult, limiting success in experiments with living organisms. In the context of T1DM, the problem is exacerbated, as chronic inflammation and autoimmune attack alter these signals, adding a layer of complexity when trying to mimic these conditions in the lab. One of the most limiting factors in developing regenerative therapies in humans is the lack of reliable tools to measure the quantity and function of beta cells. Without robust methods to measure beta cell mass and function, it's difficult to evaluate the real impact of experimental treatments and determine if observed proliferation has clinical relevance. Finally, treatments aimed at stimulating cell proliferation also carry inherent risks. Uncontrolled proliferation of beta cells could lead to problems like tumor development. In summary, the regeneration of functional beta cells remains a complicated challenge, both from a technical and biological perspective, that must be overcome before it can be applied in patients.

Even so, it's not all bad news. In recent decades, knowledge about beta cell biology and their regeneration mechanisms has advanced considerably. The field has been particularly active in seeking new strategies, such as improving preclinical models that are more representative of the human environment or applying innovative techniques like gene editing to enhance cell regeneration. Furthermore, several chemical compounds capable of inducing the proliferation of these cells in animal models and cell cultures have been identified. However, these advances have been rather modest, with results difficult to replicate in clinical trials.

In this context, a recent study has generated great interest by proposing an innovative approach that stimulates beta cell proliferation in animal models (5). To better understand its relevance, we need to go back to 2015, when a team of researchers, using a large-scale chemical compound screening technique (from a collection of over 100,000 different compounds), identified a compound that could remarkably induce human beta cell replication in cellular models: **harmine** (6). Harmine is a natural alkaloid derived from a plant called Banisteriopsis caapi, traditionally used in shamanic rituals in South America. Although this compound »

THE COMBINATION OF DYRK1A INHIBITORS AND GLP-1R AGONISTS HAS OPENED A NEW AND PROMISING AVENUE FOR REGENERATING FUNCTIONAL HUMAN BETA CELLS

» was known for its psychoactive properties, its therapeutic potential was not recognized until this study. How does harmine stimulate beta cell proliferation? Harmine acts by blocking (inhibiting, in scientific jargon) an enzyme called DYRK1A (dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A), which regulates the cell cycle. This enzyme acts as a brake on cell division. Therefore, if we inhibit DYRK1A's action, that brake is released, and beta cells can begin to multiply. This discovery led to the development of other **DYRK1A inhibitors** like 5-IT (5-iodotubericidin) which not only promote proliferation but also the differentiation and functionality of the generated beta cells. However, one of the biggest challenges with this strategy is its lack of specificity: the DYRK1A enzyme is present in many cell types, which could cause unwanted side effects.

In this new clinical trial, researchers tested a combination of these DYRK1A inhibitors with drugs that activate the **glucagon-like peptide-1 receptor** (GLP-1R) (5). These drugs, such as liraglutide and semaglutide, are widely used today to treat T2DM. These drugs do not induce proliferation of adult human beta cells on their own (though they do in rodents), but they do have high specificity for human beta cells, as GLP-1R is primarily expressed in them. The researchers discovered that using harmine with a GLP-1R analog led to greater human beta cell proliferation. One of the most important findings of this study is that they observed this not only in controlled laboratory conditions (with isolated cells in culture) but also in mice, improving their survival, functionality, and significantly increasing their number when these human cells were transplanted into the kidney. This combined treatment over three months **multiplied the number of human beta cells by 4 to 7 times**, both in healthy mice and, more importantly, in mice with severe diabetes. In other words, this strategy works in complex biological systems, a crucial step towards its possible use in patients. This remarkable increase suggests that this strategy could be sufficient to compensate for beta cell loss in people with T2DM and could even have a positive impact on T1DM if combined with therapies that control the autoimmune attack. Furthermore, the treatment was carefully designed not to affect other pancreatic cells. By using low doses of harmine and leveraging the specificity of the GLP-1 receptor, »

STOPPING THE IMMUNE ATTACK ISN'T ENOUGH: BETA CELL REGENERATION IS ALSO NECESSARY

» they managed to stimulate only beta cells, without increasing alpha pancreatic cells (which produce glucagon) or altering blood glucagon levels.

Now, this surprising increase in beta cell mass presented an enigma: although slight increases in cellular proliferation rate were observed, they didn't seem sufficient on their own to explain a growth of up to 7 times. This led researchers to wonder where all these new beta cells were coming from. A subsequent study by these same researchers has shed some light on this question (7). By analyzing human islets treated with harmine and DYRK1A inhibitors in more detail, the researchers observed an unexpected phenomenon: an increase in a subtype of cells known as "cycling alpha cells", meaning glucagon-producing cells that were actively dividing. This finding suggests that part of the increase in beta cell mass could be due to a process called **transdifferentiation**, whereby some alpha cells convert into functional beta cells. If confirmed, this mechanism would significantly expand our possibilities for regenerating beta cell mass from cells already present in pancreas.

Although these results are very promising, key questions still need to be resolved. One is whether the effects of the combined treatment will remain effective after stopping it. Will it be necessary to develop administration methods aimed exclusively at beta cells? And, above all, can these effects be reproduced in diabetic patients? Furthermore, although no significant adverse effects were observed in other tissues, long-term studies and models more similar to humans will be needed to confirm its safety. D

CONCLUSIONS

The path to a cure for T1DM requires 2 essential steps: stopping the immune system's attack and restoring functional beta cells. Recent advances have shown that this second step, something that long seemed impossible, is now a more attainable goal. The combination of well-known and clinically used drugs, such as GLP-1R agonists, with new strategies aimed at stimulating beta cell proliferation and survival using DYRK1A inhibitors, opens a hopeful door towards regenerative treatments. If these results are confirmed in human studies, we could be looking at a new option alongside other proposals, such as transplants or stem cell therapy (8, 9).

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