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Advances in cell therapy for the treatment of type 1 diabetes

Research in diabetes is progressing relentlessly, helping us improve the health and quality of life of those living with this disease. It is common for these advances to gain media attention due to their significant health care and social impact. In this regard, if we had to choose the most impactful diabetes-related news of 2024, there would likely be no debate: the report of a person in China being cured of type 1 diabetes through cell therapy. All published reviews referred to an article that appeared in October in the prestigious journal Cell (1).

But before going into detail about this advancement, I'd like to provide some context. First, and unlike what many news outlets in general media do, the first thing we must clarify is that we are going to talk about therapies aimed at type 1 diabetes mellitus. That is, those forms of diabetes in which the origin of the process lies in a poor relationship between the immune system (our defenses) and the insulin-producing cells in the pancreas (the so-called beta cells). There are other forms of diabetes for which different treatments are considered. The most common is type 2 diabetes mellitus, and for this, the approaches are completely different.

WHAT DOES IT MEAN TO TREAT TYPE 1 DIABETES WITH CELL THERAPY?

We could say that cell therapy is any therapy based on the implantation of new cells into an organism to seek the cure of a disease. In type 1 diabetes mellitus, we could make 2 broad classifications of cell therapies. First, those that use replacement cells seeking to substitute the function of the patient's beta cells blocked by the immune system's response. Second, those based on introducing into the patient's organism immune system cells different from the original ones to modify its relationship with that person's beta cells. Today, we will focus on cell therapy through the introduction of new beta cells and leave immune system cell therapy for another article.

We could say that the most "primitive" cell therapy would be that based on organ transplantation. Are organ transplants currently performed for the treatment of type 1 diabetes? Are they curative? These transplants are part of the therapeutic options in diabetes today. The complete organ transplant that could cure type 1 diabetes mellitus would be a pancreas transplant. Since we cannot transplant fractions of a pancreas from a living person, they are always performed in the context of a deceased donor. Of note, isolated pancreatic transplantation is exceptionally rare today, partly because its long-term viability is not entirely satisfactory and partly because of the advances made in recent years in advanced therapies with insulin pumps. These have made people who were previously eligible to receive them less and less common in our consultation. If a few years ago we could consider performing a pancreatic transplant in a person with type 1 diabetes mellitus who had a severe impact on their quality of life due to severe hypoglycemia, currently, we almost always find a satisfactory solution with closed-loop infusion systems. Then, are transplants no longer used in type 1 diabetes mellitus? On the contrary, we perform them in a very specific scenario: people with long-standing type 1 diabetes mellitus, but still relatively young, who unfortunately and generally due to poor diabetes control, have severe kidney damage and present or future need for renal replacement therapies (what we generally know as dialysis). Do we cure diabetes with a kidney transplant? Obviously not, but in these cases, we consider performing a double transplant, that is, we transplant kidney and pancreas synchronously or asynchronously. We do it in fact daily, although fortunately, cases are less and less common. And the most curious thing is that the long-term success of pancreatic transplantation is more promising when it is performed together with the kidney than alone. The explanation for this is that it is easier to monitor the process of kidney rejection than pancreatic rejection, but since they usually occur simultaneously, using the usual procedures that avoid kidney transplantation helps to prolong the duration of the pancreatic transplant. Here we take the opportunity to comment on something important: all cell therapies that involve the introduction of cells from another organism into a person require treatments that block the immune system. This explains, in part, why we do not consider these treatments unless the clinical situation is sufficiently complex. We must always think about the relationship of pros and cons. That said, always distrust news that headlines "first case of cure of a person with type 1 diabetes mellitus." The cure of this process is possible today, although reserved for very complex cases through transplants. We can say that the cure lasts as long as the life of the transplanted organ lasts. This has 2 major threats. We have already talked about the rejection that the recipient's defenses can generate on the transplanted organ, but let's not forget that in the case of type 1 diabetes mellitus, the immune system shows a poor relationship with beta cells and this can sprout again after a transplant. There are cases of recurrence of the immune attack on the transplanted organ. »

THERE ARE PROTOCOLS TO CONVERT SKIN FIBROBLASTS OR OTHER CELL TYPES INTO INDUCED PLURIPOTENT STEM CELLS, WHICH ARE THEN REPROGRAMMED INTO PANCREATIC BETA CELLS

» Another more "cellular" and less "organ" therapy would be the transplantation of pancreatic islets. Summarizing a lot, we can say that the goal is to avoid the technical complexity of transplanting a complete organ and its blood vessel system in people who usually have involvement of these due to the long course of diabetes. However, it has the same implications regarding the need to administer immunosuppressive treatments and a difficult graft survival in the long term. As a more negative aspect, we would have that > 1 pancreas is usually needed to obtain enough islets for a single recipient. Therefore, it is a procedure only used in a few international reference centers.

We finally come to what we would know as a true cell therapy with beta cells to treat type 1 diabetes mellitus. Where can we obtain them? Well, currently what we propose is to do it by modifying stem cells (technically known as pluripotent). Given the ethical conflicts generated by the use of embryonic stem cells and the advances made in the field of development of induced pluripotent stem cells (known by their acronym iPSC), these are the most frequently used. How are they generated? We must thank Professor Yamanaka, who received the Nobel Prize in 2012 for this reason, for the existence of a very effective protocol to convert practically any mature cell of the organism into iPSC. The most frequently used come from the skin or tissue (subcutaneous) that we have under it. Once the iPSC have been harvested, the next step is to reconvert them into beta cells. This process is also quite well established. Without being perfect, we can say that the functionality of these cells should be sufficient to consider the treatment of type 1 diabetes mellitus in people who require it. So, where is the difficulty? Well, it starts once we have beta cells "artificially" generated in the laboratory. We have said that these come from iPSC that in turn are usually generated from other cells of the organism. Here we have 2 scenarios. One more practical: we have a universal source of cells from which we obtain beta cells for all those who require it. In this case, we would have the same thing as organ transplantation, that is, we will need to apply immunosuppressive treatments to block the immune system and thus avoid rejection. On the other hand, we could make these cells come from the patient themselves. This obviously makes the process much more complex and »

BETA CELL THERAPY FROM PLURIPOTENT STEM CELLS STILL NEEDS TO OVERCOME SEVERAL BARRIERS BEFORE IT CAN BE CONSIDERED A UNIVERSAL EFFECTIVE TREATMENT

» expensive since we would have to start from scratch each case. As an advantage, we would be avoiding the risk of rejection, but as in double-edged swords, the risk of recurrence of the immune attack then appears increased.

In conclusion, the current challenge in this regard is how to infuse cells that we have in many laboratories to obtain a new source of insulin-producing cells. Here there are 2 main strategies: to generate physical barriers, membranes, that would act as a shield and allow the entry and exit of substances, but not the immune attack or, secondly, to modify the cells to avoid being recognized by the immune system. Both strategies, as always happens in research, open up additional problems and questions. Encapsulating the cells generates the problem that we limit the place of implantation of these and make it difficult in any case the irrigation of the cells and their long-term survival. For its part, modifying cells to make them invisible to the immune system avoids rejection and autoimmunity, but generates doubt about their long-term safety. Let us not forget that our immune system also protects us from cancer cells that grow uncontrollably. Any modification that avoids the interaction of the immune system with cells used in cell therapy must avoid the risk of uncontrolled growth of the same.

Let's go back to the initial case. Why was it published in the journal Cell? Well, although the media did not report it that way, it was not by any means the first cure of a person with type 1 diabetes mellitus. The true significance of the study by the group at Tianjin First Central Hospital were 2 novelties only collected in the small print of it. First, that they did not use Professor Yamanaka's protocol, but a chemical cocktail that improves the control of the stem cell generation process. On the other hand, the cells were not placed in the liver. In this case, they were transplanted into the muscle of the abdominal wall, which improves the possibility of following their progression with magnetic resonance imaging and ultrasound. Are we in any case closer to the cure? Undoubtedly yes, but let's think that this published case was already receiving treatment with immunosuppressants for other previous transplants, and that makes us unable to extrapolate its good results to a year to other cases. D

CONCLUSIONS

Cell therapy, both in its more "primitive" and more advanced modalities, are therapies with curative potential.

Currently, they are considered only for a minority of very complex cases since they are not without risk.

Therapy with beta cells produced from stem cells still needs to overcome a series of barriers to be considered as an effective treatment.

REFERENCES

1. Wang S, Du Y, Zhang B, Meng G, Liu Z, Liew SY, et al. Transplantation of chemically induced pluripotent stem-cell-derived islets under abdominal anterior rectus sheath in a type 1 diabetes patient. Cell. 2024 Oct;187(22):6152-6164.e18.