The Review of DIABETIC STUDIES

EDITORIAL

Insulin-Producing Cells from Tissue Stem/Progenitor Cells: Are Autologous Cells Preferable to Allogeneic?

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Introduction

Type 1 diabetes is caused by autoimmune destruction of the pancreatic islet insulin-producing β-cells. Insulin administration does not prevent long-term complications of the disease, since the optimal insulin dosage is difficult to adjust. Replacement of the damaged cells with regulated insulin-producing cells is considered as the ultimate cure for type 1 diabetes. Transplantation of intact human pancreas or isolated islets has been severely limited by the scarcity of human tissue donors, and the search is on for an abundant source of human insulin-producing cells. Isolated human islets have been difficult to expand in tissue culture without partial or complete loss of function. Recent progress in stem cell biology has fanned hopes for the generation of regulated insulin-producing cells by differentiation from various sources of stem/progenitor cells.

There are 2 major types of stem cells: embryonic stem (ES) cells, and tissue-derived stem cells. ES cells are pluripotent cells which can be easily propagated in tissue culture. Their spontaneous differentiation *in vitro* generates, among many cell types, a small percentage of insulin-producing cells [1, 2]. However, despite efforts to isolate these differentiated cells [3, 4], or stimulate their generation by various protocols [5], evidence is still lacking in support of their efficacy and safety in experimental models. A second type of stem cells resides in fetal and adult tissues and is responsible for tissue maintenance throughout life. These are more restricted than ES cells in their replication and multilineage differentiation capacities. However, recent reports have suggested that adult tissue stem cells can give rise to cell types from other tissues, including insulin-producing cells [6-8], given appropriate stimuli. Although findings on the physiological plasticity of tissue stem cells remain controversial, it has been clearly demonstrated that cells from tissues such as liver and intestine can be reprogrammed to assume a β-like phenotype by expression of dominant β-cell transcription factor genes [9-13]. In contrast to ES cells, tissue stem cells offer the possibility of employing autologous cells, either as a biopsy to be manipulated *ex vivo* and then transplanted into each patient, or by *in vivo* targeting of genes or differentiation factors. This possibility calls for an evaluation of the relative advantages of autologous versus allogeneic tissues in cell engineering strategies for cell replacement therapy of type 1 diabetes.

Immunological considerations

The most obvious advantage of autologous tissue is the immune tolerance to self. Thus it can be expected

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that stem/progenitor cells derived from the patient, manipulated *ex vivo* to induce their differentiation into insulin-producing cells, and returned into the same patient, will not be targeted by allograft rejection mechanisms. However, in the case of an autoimmune disease, such as type 1 diabetes, in which the patient's immune system destroys its autologous β-cells, tolerance to other self tissues which assume aspects of the β-cell phenotype may also be lost. It is quite likely that some of the antigenic targets of autoimmunity are also key components of β-cell function, and are therefore bound to be expressed in non-β-cells induced to differentiate into functional insulin-producing cells. In this case the recurring autoimmune responses against autologous cells are likely to represent a problem as difficult as allograft rejection responses. As a result, both autografts and allografts will have to be equally protected from recurring autoimmunity by a combination of approaches, including cell encapsulation, improved immunosuppression, induction of donor-specific tolerance, and cell engineering with immunoprotective genes [14]. Alternatively, it is possible that insulin-producing cells derived from non-pancreatic tissues may lack expression of the antigens targeted by autoimmunity and still perform well in terms of insulin production, storage, and regulated secretion. In this case, autologous tissues are likely to have a clear advantage over allografts. As long as the antigenic targets of autoimmunity in type 1 diabetes are unknown, this issue remains open. Animal models, such as nonobese diabetic (NOD) mice, may shed some light on it by allowing the testing of immune responses to insulin-producing cells derived from various NOD tissues. However, ultimately this issue must be addressed in clinical trials.

Practical considerations

Even if it turns out that autologous insulin-producing cells are better tolerated than allogeneic cells, a number of practical considerations may favor the use of allografts. The culture manipulations needed to induce differentiation of tissue stem/progenitor cells may be complex, and require prolonged efficacy and safety evaluations. It may be impractical or prohibitively expensive to tailor this process for each patient separately, as opposed to a cell source that is banked following a thorough characterization and ready to be used in multiple recipients. Another practical consideration relates to the tissue type that is eventually selected as the optimal source of stem/progenitor cells for differentiation into insulin-producing cells. A tissue that is relatively easily accessible for biopsy in patients, such as bone marrow, will allow the use of autologous cells. In contrast, if the tissue of choice could only be obtained from cadaver donors, it would necessitate the use of allografts. Obviously, to represent an advantage over isolated islets, the tissue of choice should be expandable in tissue culture prior to its differentiation, to provide cells for transplantation into multiple recipients. Finally, cells that undergo genetic manipulations *in vitro* may sustain chromosomal changes that would render them more prone to neoplastic transformation than normal cells. Genetically-modified cells may be approved for clinical use in certain scenarios, such as in conjunction with cell encapsulation [15]. In case of a capsule failure and cell escape, the use of autologous cells, which might not be readily rejected by the patient's immune system, could represent a greater risk, compared with that of allogeneic cells, which would be destroyed by allograft rejection immune responses.

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