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EDITORIAL

Innovative immunological strategies for type 1 diabetes☆

Estrategias innovadoras de base inmunológica en diabetes mellitus tipo 1

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The major obstacle to the development of preventive or therapeutic strategies for type 1 diabetes mellitus (T1DM) is that its etiology has not yet been elucidated. Exogenous insulin administration is the standard replacement therapy, but despite advances in this field, the achievement of adequate blood glucose control continues to be difficult for most patients. As an autoimmune disease, one of the challenges in biomedical research is to prevent the destruction of insulin-secreting β-cells. This attack by immune system cells becomes chronic and is fed back by autoantigens from the remaining and regenerating β-cells. Despite the loss of insulin production, patients retain some capacity to reconstitute the mass of β cells for many years after disease onset, which potentially prolongs the immune intervention period.

In recent decades, many clinical trials based on immunotherapies have been conducted to prevent, stabilize, and even reverse T1DM. The objective of these trials was to stop autoimmune aggression and recover β-cell tolerance. Some examples include therapy with molecules that inhibit the autoimmune response with β-cell autoantigens or immunoregulatory cytokines. Many of these strategies had previously been successfully tested in the experimental model of the disease, the nonobese diabetic mouse, which develops spontaneous autoimmune diabetes. This model has been a helpful tool for studying the disease and developing immunotherapies, and has generated a body of knowledge difficult to obtain in human T1DM because of its asymptomatic phase and the inaccessibility of the target organ, i.e. the pancreas. Clinical trials to determine the preventive or therapeutic capacity of these immunotherapies have required great scientific and financial effort. Unfortunately, the results have been disappointing, partly because of differences between the murine model and human disease.[1] No immunotherapy has been able to permanently prevent or reverse the disease, and some of them have caused significant side effects.[2] However, these trials have made it possible for some conclusions regarding the impact of immunotherapies on the course of T1DM to be drawn.

The first therapeutic trials with cyclosporine were conducted in the mid-1980s. This immunosuppressant drug was able to reverse the disease, thus confirming the immune-mediated nature of T1DM. However, the risk of cyclosporine nephrotoxicity and its effect on the immune system precluded treatment. In the last decade, clinical trials have been conducted with multiple immunomodulatory strategies,[3] among which anti-CD3 monoclonal antibodies, directed against T cells, deserve special mention. In nonobese diabetic mice, this immunotherapy achieved total disease remission, and the humanized versions of the antibody (teplizumab and otelixizumab) tested in patients with T1DM of recent onset preserved the residual beta-cell mass, but had significant adverse effects.[4] Other immunotherapies followed based on the blockade of CD20 molecules in B cells (rituximab),[5] the blockade of the costimulatory signal using CTLA4 (abatacept),[6] or a combination of anti-thymocyte

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globulin with granulocyte colony-stimulating factor.[7] Overall, the results of these systemic immunotherapies have been disappointing. On the other hand, therapies with autoantigens such as insulin itself in multiple forms,[3] glutamic acid decarboxylase conjugated with aluminum,[8] or a peptide of the heat shock protein Hsp-60 (the DiaPep277 peptide)[9] have not reversed the disease either. Some strategies, however, have been able to protect the function and mass of residual β-cells, suggesting that the autoimmune attack had been repulsed, although the improvement does not lead to clinically significant results in the short term. It remains to be established whether or not these immunotherapies ameliorate the long-term secondary complications. Since 1998, preventive clinical trials have also been conducted using nicotinamide, autoantigens (glutamic acid decarboxylase, insulin), antibodies (anti-CD3, abatacept, anti-IL1), cytokines,[3] or dietary interventions (gluten-free diet or diet with hydrolyzed casein).[10] No conclusive data supporting these therapies currently exist, but some of them appear to delay disease onset.

Analysis of the results of some of these trials did not allow for any conclusions to be drawn because of problems in trial design and adverse effect identification, and because disease heterogeneity had not been considered. These errors will hopefully be avoided in the future, and the knowledge gained from ongoing multicenter studies and collaborative networks focused on disease etiology should be applied. These studies, the Network for Pancreatic Organ Donors with Diabetes (nPOD), The Environmental Determinants of Diabetes in the Young (TEDDY), the Diabetes and Autoimmunity Study in the Young (DAISY), All Babies in Southeast Sweden (ABIS), the Persistent Virus Infection in Diabetes Network (PevNet), and the Diabetes Virus Detection Study (DiViD),[11] address various issues and apply innovative technologies, and may therefore be expected to contribute to further elucidating the causes of T1DM. At the same time, there is work ongoing to define better biomarkers of β-cell destruction and regeneration in peripheral blood. Both aspects will be determinant in improving the application and monitoring of these therapies.

The problem of β-cell autoimmunity is currently being addressed with new immune-based approaches, most of them experimental, although there are also some clinical trials ongoing. In the recent congress of the Immunology of Diabetes Society, held in Munich in April 2015 (www.ids2015.org), a trial of administration of very low IL-2 doses as a systemic strategy to expand regulatory T cells was presented (www.diabil-2.eu).[12] This trial also addresses other autoimmune diseases such as lupus, autoimmune vasculitis, and alopecia areata. As regards T1DM, the trial has recruited pediatric patients with disease onset less than two months before, who will receive treatment for one year. Preliminary results indicate the expansion of $Foxp3^+$ regulatory T cells, both $CD4^+$ and $CD8^+$, as well as increased plasma levels of regulatory cytokines. The need to take into account seasonal variations in the expression of autoantigens and immune response genes, including IL-2,[13] in these new trials has also been discussed.

Cell therapy is another innovative field where leukapheresis and *in vitro* manipulation of immune system cells are performed. Since dendritic cells play a significant role in the regulation of immune response, one strategy consists of harvesting autologous tolerogenic dendritic cells able to perform suppressive antigen presentation that inactivates autoreactive T cells. These cells have preventive and therapeutic capacity in experimental diabetes. There have been improvements in the harvesting of human dendritic cells in recent years, and a clinical trial has been started with this type of therapy.[14] On the other hand, a recent clinical trial with 12 pediatric patients using autologous regulatory T cells, expanded *in vitro*, showed increased C peptide levels and decreased exogen insulin requirements, and disease remission was achieved in two patients.[15] Another innovative cell therapy trial is the so-called Stem cell educator, which consists of recirculating blood from the patients through a culture of immunomodulatory stem cells from the umbilical cord and returning it to the patient's circulation. The trial – in which Hospital Universitario Central de Asturias is participating – shows that treatment is well tolerated, generates regulatory T cells, and improves C peptide production, decreasing insulin requirements.[16] The action mechanisms of these treatments are being studied.

Bioengineering and nanotechnology are additional fields where work is ongoing to develop innovative therapies which are currently in the preclinical phase.[17] Special mention should be made of the engineering of autoantigens for erythrocyte binding, intended to induce specific tolerance by apoptosis and to contribute to arresting autoimmunity.[18] As regards nanotechnology, it is used to modulate the autoimmune response on a nanometric scale. Its advantages include the need for lower drug doses and the possibility of direcing the molecule to the cell of interest. Iron oxide nanoparticles coated with molecules of the major histocompatibility complex with autoantigens, which generate regulatory $CD8^+$ T cells and reverse experimental T1DM, are of special interest.[19] Microspheres containing oligonucleotides to block antigen presentation have also been designed.[20] More recently, liposomes that mimic apoptotic β-cells to arrest specific autoimmunity and induce tolerance by molecular mimicry have been devised.[21]

We think that efforts should be made to optimize immunotherapies by addressing T1DM as a whole, that is, by taking into account inflammation, specific autoimmunity, and attempts at β regeneration. Therapies should be administered by the best route, without compromising immune system function and in combination with regenerative strategies, while bearing in mind the heterogeneity of human disease. The identification of prediabetic subjects based on new biomarkers would also allow us to take action in the preclinical phase, which would undoubtedly increase the chances of success. Advances in this area are slow, but a trend to immunometabolic improvements has been seen in some phase 2 clinical trials in recent years. Elucidation of the causes of T1DM and the identification of better biomarkers of disease progression will undoubtedly contribute to the optimization of immunotherapies, so enabling us to win the battle against this disease.

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