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Immunity in the early diagnosis of type 1 diabetes and therapeutic strategies

Type 1 diabetes (T1DM) is an autoimmune disease in which the body's own immune system attacks the beta cells of the pancreas. These cells are responsible for producing insulin, so their destruction leads to a lack of this hormone, which prevents the body from using glucose. However, T1D begins long before this lack of insulin is evident.

PROGRESSION OF T1DM

There is a **genetic predisposition** to develop T1DM, mainly determined by the human leukocyte antigen (HLA) type 2. An unknown environmental trigger acts upon this genetic predisposition, initiating the autoimmune process. T1DM begins from the start of this autoimmune attack, and we can distinguish several phases within it:

Phase 1: Positive Autoimmunity

The autoimmune process that leads to T1DM is a process of cellular attack by T lymphocytes. The detection of **autoantibodies** against pancreatic beta cells indicates that the immune system is reacting against them even before symptoms related to insulin deficiency appear.

There are four autoantibodies that will signal this autoimmune attack:

- Against insulin (IA).
- Against the glutamic acid decarboxylase enzyme (GAD).
- Against tyrosine phosphatase 2 (IA-2A), a membrane protein of beta cells.
- Against zinc transporter 8 (ZnT8).

The risk of progression to more advanced phases of T1DM will depend on:

- The type of autoantibody that is positive: positivity for anti-IA-2A antibodies implies a higher risk of progression than positivity for anti-GAD or anti-IA2 antibodies.
- The antibody titer: the higher the titer, the greater the risk.
- The number of autoantibodies that are positive: the more autoantibodies, the greater the risk.

Phase 2: Dysglycemia

The transition to phase 2 of T1DM occurs when, in addition to pancreatic autoimmunity, dysglycemia appears, understood as an alteration in glucose levels not as marked as that which occurs in the clinical diagnosis of DM.

Phase 3: Clinical Diagnosis of T1DM

Phase 3 is reached when the clinical diagnostic criteria for T1DM are met. The latest clinical practice guidelines from the International Society for Pediatric and Adolescent Diabetes (ISPAD) distinguish two phases: phase 3A, when the patient remains asymptomatic and does not require insulin, and phase 3B, where insulin use is already necessary.

THERAPEUTIC STRATEGIES

Traditionally, T1DM has been treated with insulin replacement therapy, either with multiple daily injections using pre-filled pens or through insulin infusion systems. This strategy does not address the underlying problem of autoimmunity that causes T1DM. Advances in the pathophysiological understanding of T1DM have opened the door to treatment in preclinical phases to halt autoimmunity and **preserve the function** of pancreatic beta cells.

Initially, classic immunosuppressive agents (cyclosporine, azathioprine, prednisone) were tested, but this strategy was stopped when it was found that the side effects of immunosuppression were greater than the benefits obtained.

Phase 1

When individuals in phase 1 are detected, the goal is to prevent the onset of dysglycemia. Strategies tested in this phase have tried to induce **immunological tolerance**, using some of the main autoantigens. Oral or intranasal insulin and the GAD65 antigen have been used within these strategies, although the results obtained so far have not been conclusive.

Phases 2 and 3

When we encounter people in phase 2, the treatment should prevent the onset of clinical T1DM. In phase 3, the objective is less clear. Some authors suggest slowing down the reduction of C-peptide; others propose that people stop needing insulin or reduce it, and others that HbA1c be reduced.

Many of the drugs tested in phase 2 are also being studied in phase 3, since the common goal of both phases **is to halt the destruction of beta cells**.

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THE EVOLUTION IN THE PHYSIOPATHOLOGICAL KNOWLEDGE OF T1DM HAS OPENED THE DOOR TO TREATMENT IN PRECLINICAL PHASES TO HALT AUTOIMMUNITY AND PRESERVE THE FUNCTION OF PANCREATIC BETA CELLS

TEPLIZUMAB, A MONOCLONAL ANTIBODY AGAINST CD3, IS THE FIRST DRUG APPROVED IN THE UNITED STATES TO DELAY THE PROGRESSION FROM STAGE 2 TO STAGE 3 IN INDIVIDUALS OLDER THAN 8 YEARS

THERAPIES TARGETING CD3

CD3 is an antigen on the surface of T lymphocytes that is part of the receptor complex of these lymphocytes. Blocking it inhibits the activation of autoreactive T lymphocytes and the destruction of pancreatic beta cells.

Teplizumab, a monoclonal antibody against CD3, is the first drug approved in the United States to delay the progression from phase 2 to phase 3 in individuals older than 8 years.

The clinical trials that allowed its approval demonstrated that the median progression to phase 3 in those who recei-

» ved intravenous teplizumab for 14 days occurred 2 years later than in those who received placebo.

A different anti-CD3 tested in this phase has been otelixizumab.

Within the group of therapies that act on T lymphocytes, we can mention thymoglobulin, already proven in anti-rejection therapies for transplantation and capable of eliminating T lymphocytes, thus reducing autoimmunity.

Therapies targeting B lymphocytes

B lymphocytes serve as antigen-presenting cells and act by producing antibodies. One of the drugs tested in phase 3 with limited results has been rituximab. This molecule binds to the CD20 antigen, present on the surface of B lymphocytes, leading to the destruction of these lymphocytes and reducing the production of autoantibodies.

Cytokine-based therapies

Cytokines are mediators of the interaction between the immune system and pancreatic cells.

There are cytokines that promote inflammation, such as tumor necrosis factor alpha (TNFα), interleukin 1 (IL-1), and IL-6. In these cases, therapies aim to inhibit these pro-inflammatory cytokines, such as etanercept or golimumab (TNFα inhibitors), anakinra (IL-1 inhibitor), or tocilizumab (IL-6 blocker).

Many cytokines exert their inflammatory activity when, upon binding to their receptor, they send an intracellular signal through the janus kinase (JAK) cell signaling pathway. Therefore, other therapies have focused on inhibiting this intracellular inflammation signaling pathway. The results of baricitinib stand out here, as well as other molecules under study such as abrocitinib and ritlecitinib.

Side effects

The use of all these therapies is not without side effects. In addition to possible local reactions, the most frequent adverse effects are an increased risk of infections or the reactivation of latent infections.

UNRESOLVED ISSUES AND FUTURE THERAPIES

The treatment of T1DM in preclinical phases raises unresolved questions: it remains to be determined **when is the ideal time** to administer these therapies, whether the **combination of therapies** or their periodic administration can improve results, **or what patient profile responds best**.

Other therapies are under study, such as those that use **plasmids** to transfer DNA encoding proteins that promote tolerance to autoantigens and modulate the immune response, or the **transplantation** of pancreatic islets in encapsulated vectors that avoid the need for immunosuppression. Another field to explore is the use of Chimeric Antigen Receptor T-Cell Therapy **(CAR-T)**. In this therapy, the patient's own T lymphocytes are genetically modified to more effectively attack a target, which in the case of autoimmune diseases such as DM1, would be autoreactive T lymphocytes. D

CONCLUSIONS

The greater understanding of T1DM has opened a new possibility for treatment in the preclinical phases of the disease with the aim of reducing the destruction of beta cells and avoiding dependence on exogenous insulin.

The focus of treatment is shifting from tertiary prevention, which administers the insulin that is no longer produced, to a primary prevention approach that prevents a deficit in insulin production from occurring.

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