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Autoimmunity and Therapeutic Challenges of Type 1 Diabetes

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Type 1 diabetes (T1D) is a T cell-mediated autoimmune disease that reduces the population of pancreatic islet β cells and thereby limits insulin production and glucose homeostasis. Millions of individuals worldwide have T1D, and the number of individuals with diagnosed or undiagnosed T1D is increasing annually. While daily insulin injections offer some control over blood sugar levels and may delay the onset of chronic diseases initiated by glucose dysregulation, insulin supplementation is not a cure. It does not halt the persistent autoimmune response, nor can it reliably prevent devastating complications such as neuronal and cardiovascular diseases, blindness, and kidney failure. A true cure has proven elusive despite intensive research pressure over the past 25 years, and the failure of several recent clinical trials that were based on preliminary success in animal models [1-4] further highlights the challenges we face in conquering this disease. However, even these failures provide some valuable lessons about the limitations and future directions of the quest.

Among animal T1D models, nonobese diabetic (NOD) mice have been particularly useful in studies of T1D pathogenesis and drug development [5-8]. NOD mice spontaneously develop an immune-mediated T1D that closely resembles human T1D, providing a seemingly ideal test bed for studying autoimmune therapies. However, recent clinical trials based on preliminary studies in NOD mice have not been successful, and mounting evidence suggests this is attributable to key differences between human and rodent immune systems. NOD mice and other rodent models are thus unlikely to provide reliable guidance for the development of new therapies. Instead, we need a new model or models of human immunocyte-mediated disease that can serve as a reliable tool or tools for modern translational research [7-9].

Ideally, therapeutic approaches to treating or curing T1D should address multiple or all of the underlying causes of autoimmunity in T1D. Unfortunately, the etiology of T1D remains largely unknown in humans. Possible triggers for autoimmunity in T1D include genetic, epigenetic, physical, social, and environmental factors. These factors may act independently or jointly to initiate or potentiate the development of autoimmunity. As is expected in conditions with multiple contributing factors, T1D-related dysfunction in the immune system has been traced to dysfunctions in multiple cell types and targets including T cells, B cells, regulatory T cells (Tregs), monocytes/macrophages, dendritic cells (DCs), natural killer (NK) cells, and natural killer T (NKT) cells [10]. Due to the polyclonal nature of T1D-related autoimmune responses and the global challenges of immune regulation in T1D patients, therapies and trials that only target one or a few components of the autoimmune response are likely to fail just as recent trials involving anti-CD3 Ab for T cells and GAD 65 vaccination have failed [2-4]. Successful therapies will likely restore immune balance and peripheral tolerance by addressing changes in multiple targets within the immune system.

We do know that regulatory T cells (Tregs) play a key role in T1D-related autoimmunity. These cells, as well as regulatory B cells (Bregs), regulatory dendritic cells, and regulatory macrophages control both the adaptive and innate immune responses. Tregs play an essential role in limiting the development and persistence of autoimmunity by controlling immune homeostasis and self-tolerance. Specifically, Tregs typically exert inhibitory control over autoreactive effector T cells [11-17] by releasing immunosuppressive cytokines interleukin-10 (IL-10) and/or transforming growth factor-β (TGF-β). Although defects of effector T cells [18-21] or antigen-presenting cells [22-26] could play a role in the development of T cell-mediated autoimmunity in T1D, evidence from both animal models and individuals with T1D point primarily to abnormalities of Tregs, including cell number [27-29] and function [13,30-35]. The manipulation of Tregs and/or other regulatory immune cells offers an attractive possibility for conferring protection against autoimmune-initiated T1D.

Islet transplantation, drug-mediated promotion of β-cell regeneration, and stem cell transplantation have been proposed and tested as likely approaches for treating T1D. However, the continued presence of autoreactive effector T cells and B cells in the circulation may destroy insulin-producing cells generated through these approaches, thereby minimizing their therapeutic potential. An alternative approach using *ex vivo* co-culture of immune cells with stem cells holds promise for addressing both persistent autoimmunity and the regeneration of insulin-producing β cells.

Certain adult stem cells possess the capacity to modulate the immune response of circulating immune cells. Human multipotent cord blood stem cells (CB-SCs) [36,37] and mesenchymal stem cells [38] retain this capacity even after *in vitro* clonal expansion. Recent studies demonstrate that these cells can modulate the immune response of $CD4^+$ T cells, $CD8^+$ T cells, B cells, monocytes/macrophages, DCs, and NK cells [39,40]. We have also demonstrated that CB-SCs can correct functional defects in mouse $CD4^+CD62L^+$ Tregs leading to reversal of overt diabetes in NOD mice [36]. However, recent findings from other studies based on results in mouse models suggest that our results in NOD mice should be reviewed with some caution.

We recently developed a novel therapy based on our results in NOD mice and other evidence that CB-SCs can control autoimmune responses by altering Tregs and human islet β cell-specific T cell clones [36,41,42]. In this therapy, a novel device (the Stem Cell Educator) functions as part of a closed-loop system that circulates a patient's blood through a blood cell separator, briefly co-cultures the patient's lymphocytes with adherent CB-SCs *in vitro*, and returns the educated lymphocytes (but not the CB-SCs) to the patient's circulation. CB-SCs attached to interior surfaces in the device present secreted and cell-surface signaling molecules to passing lymphocytes, and only the autologous lymphocytes are returned to the subjects. Findings from ongoing clinical trials provide powerful evidence that a single treatment with the Stem Cell Educator provides lasting reversal of autoimmunity that allows regeneration of islet β cells and improvement of metabolic control in individuals with long-standing T1D. Findings from these

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trials indicate that CB-SC-mediated reversal of autoimmunity results from modulation of the immune response in multiple immune cell types, thereby meeting the expectation that successful therapies will likely address multiple sources of the autoimmune response. These findings provide a much-needed boost for T1D therapeutic research. In addition, the broad, non-specific modulation of autoimmunity provided by the Stem Cell Educator may also be successful in treating other autoimmune diseases while mitigating the safety and ethical concerns associated with current conventional immunotherapy.

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