Thoughts on the Pathogenesis of Type 1 Diabetes and on the Arrest of Autoimmune Beta-Cell Destruction by Peptide p277 Vaccination

Irun R. Cohen MD

Department of Immunology, Weizmann Institute of Science, Rehovot, Israel

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Type 1 diabetes results from the destruction of beta cells by an autoimmune attack. Hence, any cure of type 1 diabetes should include permanent arrest of the autoimmune attack before the irreversible destruction of beta cells has taken place. Here I refer to an approach to curing type 1 diabetes using vaccination with a peptide, p277, from the sequence of the 60 kD heat shock protein [1]. I shall discuss difficulties in understanding the cause of type 1 diabetes, the pathophysiology of the autoimmune process, and the mechanism by which vaccination with peptide p277 arrests beta-cell destruction. In closing, I shall introduce a general idea aimed at making sense of these perplexing processes. Specific information about type 1 diabetes can be found in various reviews [2], and the development of p277 vaccination has also been reviewed [3].

Cause of type 1 diabetes

The cause of a disease is clearest scientifically if we can blame one or a few specific genes (a genetic disease); a specific virus, bacterium or other parasite (an infectious disease); a specific injury (a traumatic disease); a defined cellular transformation (a hyperplasia or a neoplasia); a mishap in specific organogenesis (a developmental disease); exposure to a particular toxin (an intoxication); a lack of a defined essential nutrient or an excess of a foodstuff (a dietary disease); or a cognitive malfunction (a mental disease). Type 1 diabetes, like most other autoimmune diseases, presents a nosologic difficulty: an autoimmune process perpetrates the damage, but we usually cannot assign the onset of the disease to a specific factor or factors. Indeed, too many causative factors seem to be implicated in autoimmune diseases. Certain genes contribute to susceptibility (or to resistance), but most persons who have inherited susceptibility genes will never express the illness. Infections with different viruses have been implicated in selected cases of diabetes, but most persons developing the autoimmune disease show no evidence of the suspect viruses. Defined toxins can trigger the autoimmune process in some situations, but not in very many. The rising incidence of type 1 diabetes in advantaged populations suggests that multiple factors associated with well-being can be detrimental. Not only is the induction of the destructive autoimmune process a mystery, the natural history of the autoimmune process itself is difficult to understand.

Autoimmune pathophysiology

The concept of clonal selection attributes any autoimmune disease to the emergence of a single aberrant lymphocyte clone that recognizes and attacks a disease-specific target self-molecule [4]. But type 1 diabetes, like other autoimmune diseases, is marked by a collective of many autoimmune clones that recognize many different target molecules, and some of these molecules are not expressed only in the organ under attack. About a dozen different self-antigens have been implicated in type 1 diabetes, and only insulin among them is specific to beta cells [2]. There are many false positive subjects: persons with autoimmunity to insulin or other disease-associated antigens may never come down with type 1 diabetes. Some types of insulitis (peri-islet infiltrates) can persist for long periods with no apparent beta-cell destruction; what keeps the inflammatory cells peri-islet and then what triggers them suddenly to penetrate the islet (intra-islet insulitis) and kill beta cells? How do the alpha and gamma cells escape while the beta cells are destroyed? In short, we do not really know what initiates the autoimmune disease process and, once initiated, what determines whether the autoimmune infiltrate will damage or not damage the beta cells.

Peptide p277 vaccination

Fortunately, one can educate the immune system, like one can educate the brain, without knowing in exact detail how the system works. My colleagues and I discovered that peptide p277 of the HSP-60 molecule was targeted by a clone of non-obese diabetic mouse T cells that could adoptively transfer insulitis and hyperglycemia in mice [5]. We did not have to know the role of HSP-60 or of p277 in the pathogenesis of type 1 diabetes in mice to learn that administration of HSP-60 or of p277 could arrest the spontaneous destruction of beta cells in NOD mice [6]. Curiously, vaccination with p277 [7] or with HSP-60 [8] induced a change in the expression of the autoimmunity not only to p277 and HSP-60 but also to other antigens in the diabetes collective such as insulin and glutamic acid decarboxylase. T cell autoimmunity to these

HSP-60 = 60 kD heat shock protein
NOD = non-obese diabetic

antigens switched from a damaging Th1 type of response to a protective Th2 type of response [1,7,8]. Immunity to foreign antigens, however, remained in the desirable Th1 mode. Requisite toxicology studies and phase 1 human trials set the stage for placebo-controlled phase 2 studies in patients with new-onset type 1 diabetes, and the results indicated that vaccination with peptide p277 could successfully arrest beta-cell damage [1]. But we have no information to account for the ability of a single peptide such as p277 to induce a Th2 shift in the autoimmune phenotype and arrest the progression of damage.

Immune body image

Type 1 diabetes confronts us with conceptual problems at each of its stages. Although much deserves to be discussed in detail, I have space here only to suggest a general idea about autoimmunity in type 1 diabetes and in other diseases in the light of ideas about the brain brought to my attention when reading a book by Antonio Damasio [9]. Damasio explains that creatures with brains manage their lives by deploying dynamic maps (formed by neuronal circuits) of the state of one's own body and of the effects of the environment on one's body states. But brain maps not only record the state of the body, the nature of one's neuronal circuits can itself change the state of one's body; indeed, the body can be affected adversely by defective or "false" maps of what the true state of the body should be (imagination can lead one astray).

Now the immune system, too, manages aspects of the body by mapping the state of the body using immune networks; I have termed such maps (produced by natural autoimmunity) "the immunological homunculus" [10]. But like the brain, the maps of the immune system not only map the state of the body, they affect the body. By dispensing and regulating the processes we call inflammation, the immune system heals wounds, stimulates regeneration of tissues, disposes of waste, kills dangerous body cells and rejects invading agents [11]. Inflammation managed by the immunological homunculus maintains us despite the wear and tear of existence. The properly performing homunculus promotes health. But, like the brain, the immune system can create a false map of the state of the body, and so damage body organs by misdirected inflammation; inflammatory molecules and cells of the inappropriate type, in wrong amounts, with wrong dynamics, or expressed at wrong sites can cause type 1 diabetes and other autoimmune diseases. Vaccination (immune education), however, can induce the immunological homunculus to mend its ways: witness p277.

Obviously, such a general analogy between the strategy of the brain and that of the immune system will not cure or alleviate any real disease. Nevertheless, general ideas and metaphors can stimulate good experiments. The immune system, like the brain, is a complex cognitive system, and we can profit from parallel thoughts about both [12].

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Correspondence: Dr. I.R. Cohen, Dept. of Immunology, Weizmann Institute of Science, Rehovot 76100, Israel.
Phone: (972-8) 934-2911
Fax: (972-8) 934-4103
email: Irun.cohen@weizmann.ac.il