Arresting Beta-Cell Destruction in Type 1 Diabetes Mellitus: Mobilizing Homuncular Autoimmunity to Treat Autoimmune Disease

Irun R. Cohen MD

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

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The immunological Homunculus – or Immunculus – designates particular sets of self-antigens to which healthy individuals manifest autoantibodies and autoreactive T cells [1-3]. We recently demonstrated in a phase 3 clinical trial that the subcutaneous administration of 1 mg of a self-peptide three times a year to patients with new-onset type 1 diabetes mellitus (T1D) could significantly arrest the autoimmune destruction of their residual beta cells and enhance metabolic control of their diabetes – all with apparently no undesirable side effects [4]. The effective peptide p277 (in DiaPep277) is derived from the human heat shock protein-60 (HSP60) molecule; how can so small a dose of a self-peptide antigen have such a marked effect on an advanced autoimmune process? Here, I will briefly summarize the fact that the p277 peptide of human HSP60 is a homuncular self-antigen. The p277 peptide treatment of T1D evolved over 20 years of basic and clinical research [5], but the take-home lesson is clear: Homuncular autoimmunity can be mobilized to safely and effectively treat a serious autoimmune disease; in place of global suppression of the immune system with its attendant toxicity, we can now reason with the system, as it were, using its own molecular language.

THE AUTOANTIBODY HOMUNCULUS

A global view of natural autoantibodies capable of binding to self-antigens was first obtained using gel-separated extracts of healthy tissues arrayed on gels [2]. This "Panama Blot" technology paved the way for the development of microarray devices that could test microliter volumes of fluid for the binding of antibodies and autoantibodies to hundreds of known proteins, peptides, lipids, carbohydrates, and nucleic acids arrayed on glass slides [6]. Examination of sera from healthy persons, including young mothers and their newborn babies (cord blood), helped characterize the basic autoantibody Homunculus. Human babies obtain from their mothers immunoglobulin (Ig) G autoantibodies to many self-antigens; however, newborn humans during healthy development in utero actively produce IgM and IgA autoantibodies to common sets of self-antigens – a congenital Homunculus [6].

The point here is that HSP60 and its p277 peptide are prevalent homuncular self-antigens. Indigenous homuncular autoimmunity can be beneficial; the presence in unimmunized NOD male mice of antibodies to HSP60 peptide p277 was correlated with natural resistance to the development of T1D [7].

THE AUTOREACTIVE T CELL HOMUNCULUS

It is only recently that advances in sequencing and informatics analysis have made it possible to characterize T cell repertoires. My laboratory has collaborated with Nir Friedman and his group to study the CDR3 segments of the T cell receptor (TCR) beta chain repertoire in 28 healthy C57BL/6 mice. It turns out that several hundreds of public CDR3 segments are shared by all, or almost all mice [8].

We found that the TCR CDR3 sequence (C9) of NOD mice that responds to HSP60 peptide p277 [9] was also a public TCR segment in our database of healthy C57BL/6 mouse T cell repertoires [8]. The C9 sequence manifests a large clone size and a high degree of convergent recombination. Because of the degeneracy of the nucleic acid codons for each expressed amino acid, the C9 sequence is encoded by an average of over 50 different nucleic acid sequences; private CDR3 segments are encoded by one nucleic acid recombination, on average [8]. Thus, HSP60 and its p277 peptide are members of a highly shared public TCR repertoire prevalent in variously different mouse strains. It appears that major histocompatibility complex differences are reflected more in V-gene usage than in CDR3 segments [8].

A SHIFT IN PARADIGM

Initially, self-reactive lymphocytes were thought to be forbidden [10]; we now know that self-recognizing T cells and B cells, components of the Homunculus, are present from birth in all individuals. Indeed, there seems to be strong positive selection

for public autoreactive repertoires [8]. The recent observation that one such public homuncular peptide epitope, p277, can signal the immune system to desist from an autoimmune attack in T1D [4] suggests that some homuncular self-antigens may function as immune modulators. The immune system responds to these self-molecules as biomarkers for regulating inflammation; indeed, the immune system seems to be poised to recognize HSP60 and peptide p277 using many different receptors, innate TLR as well as somatically generated antigen receptors. Whether homuncular self-molecules can be used to treat other autoimmune diseases is an open question; we are now developing treatments based on HSP70 and HSP90 homuncular molecules.

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

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