PERSPECTIVES: IMMUNOLOGY

GAD, a Single Autoantigen for Diabetes

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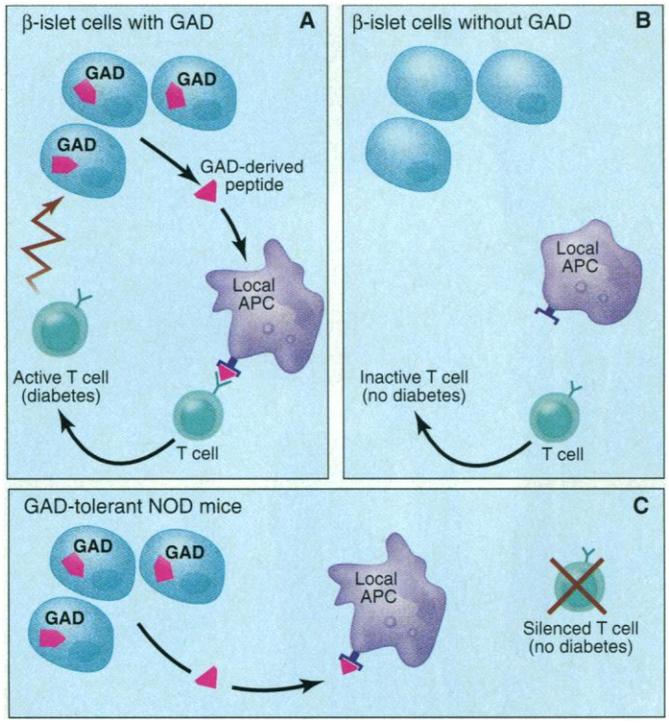
Type I diabetes is an autoimmune disease that affects 0.3% of the world's population. It is caused by autoaggressive T cells that infiltrate the pancreas and eventually destroy the insulin-producing β-islet cells. This results in an increase in glucose levels, which are normally kept in check by insulin. Autoimmune diabetes usually affects young people, who are then dependent on an artificial source of insulin for life. The identity of the self proteins in the pancreatic islets that target the cells for autoimmune destruction has long been debated. On page 1183 of this issue, Yoon *et al.* report a real breakthrough in understanding the etiology of type I diabetes (*1*). They show that a single self protein expressed by β-islet cells, glutamic acid decarboxylase (GAD), controls the development of diabetes in the nonobese diabetic (NOD) mouse (a good animal model of human type I diabetes).

There are two forms of GAD, GAD65 and GAD67, and both forms are expressed in brain cells (where they are involved in production of the neurotransmitter GABA) and in β-islet cells, where their function is not clear (*2*). GAD65 has come under the scrutiny of diabetes researchers because some of the earliest autoantibodies found in prediabetic patients are GAD-specific, although other autoantibodies, such as those directed against insulin, are also present (*3*, *4*). Furthermore, intrathymic, intravenous, or oral administration of GAD65 has, in some instances, significantly delayed the onset of disease in NOD mice (*5*–*9*). Although intriguing, these observations still do not implicate GAD in the initiation of the disease process.

The simple and bold strategy adopted by Yoon *et al.* was to determine whether the development of diabetes in NOD mice required the expression of GAD. They accomplished this by generating transgenic NOD mice that expressed a GAD antisense gene exclusively in β-islet cells such that expression of both GAD isoforms was prevented in these cells (but not in brain cells). This strategy would have failed if GAD had an essential function in β-islet cells, which apparently it does not. The investigators were thus able to observe a strict correlation between the presence of GAD protein in β-islet cells and the development of diabetes. In those animals that efficiently expressed the antisense transgene, there was no β-islet GAD expression, and the mice remained free of diabetes (see the figure). In contrast, mice that poorly expressed the transgene or that expressed a transgene with irrelevant information became diabetic. Furthermore, the autoimmune inflammation of salivary glands (which do not express GAD) that is normally observed in NOD mice was not diminished by efficient expression of the antisense transgene. So, the specific absence of GAD in β-islet cells offers the cells protection from autoimmune attack. The authors go on to show that because of the absence of GAD in β-islet cells, there was no anti-GAD T cell response. T cells from GAD-less NOD mice (in contrast to those from animals expressing GAD in β-islets) did not transfer the disease when injected into T cell–deficient NOD mice. Moreover, when transplanted into diabetic NOD mice, GAD-less islet cells but not normal islets were spared from immune attack. Finally, there were fewer T cells reactive to other β-islet–specific autoantigens such as insulin in GAD-less NOD mice but not in nontransgenic control animals. These results show that GAD is the essential autoantigen that initiates the disease by activating GAD-specific T cells. As the disease progresses, T cells reactive against additional β-islet–specific antigens become activated.



Gadfly autoantigen. Autoimmune diabetes develops in nonobese diabetic (NOD) mice when peptides derived from glutamic acid decarboxylase (GAD), which is expressed by the insulin-producing β-islet cells (blue) of the pancreas, are presented by antigen presenting cells (APCs) to T cells (**A**). These T cells become activated and destroy the β-islets, resulting in the loss of insulin and the development of diabetes. In transgenic NOD mice with islet cells that do not express GAD, the relevant T cells are not activated, and diabetes does not develop (**B**). If it were possible to eliminate or silence GAD-specific T lymphocytes by inducing expression of GAD in all cells, then diabetes should not develop (**C**).

The demonstration that a single self protein initiates autoimmune diabetes could have important consequences for therapeutic strategies—provided, of course, these findings can be extended to the human disease. It is likely that GAD is also the initiating autoantigen in human type I diabetes because GAD-specific autoantibodies are among the first to appear in the prediabetic phase in human patients. Transplantation of human islets rendered GAD-less by introduction of an antisense transgene in vitro might benefit diabetic patients. Alternatively, if the relevant GAD autoantigenic peptides were expressed in all tissues of the body, including the thymus, it may be possible to induce GAD-specific tolerance. It is conceivable that such an approach might eliminate type I diabetes from the human population. This is not a new idea; several groups have generated NOD mice with ubiquitously expressed transgenes. Surprisingly, in light of the

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Yoon results, these animals still developed diabetes. In fact, it was found that the mice were not tolerant to GAD (*10*, *11*). One study showed that despite the presence of the entire GAD protein in hematopoietic cells, autoantigenic GAD peptides were not presented on the surface of these cells (*11*). Thus, the GAD in pancreatic islet cells may be proteolytically cleaved to generate a completely different set of peptides not found in other cells. Given the results presented in the Yoon report, it may be worthwhile to express the relevant GAD epitopes before the immune system develops, thereby inducing effective tolerance by intrathymic deletion of immature T cells (*12*, *13*). This would require inserting a transgene into the germ line, clearly taboo in humans. To treat human diabetes in this way one would have to effectively induce tolerance in mature T cell populations in young individuals with a genetic predisposition to the disease. This is not easy: Tolerance induction in mature T cells is often preceded by a brief effector phase before the T cells become anergic or are deleted, which would pose a risk of accelerating the disease (*14*, *15*).

The finding by Yoon *et al.* that GAD is the initiating antigen of autoimmune diabetes is a major step toward formulating new therapies to treat this disease. The invaluable NOD mouse will enable the benefits of these new therapeutic strategies to be firmly established before their application in humans.

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PERSPECTIVES: CONDENSED MATTER PHYSICS

Is This Why T_c Is So Low?

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Early in the effort to understand high–transition temperature (T_c) superconductors, Lee and Read asked a provocative question: Why is the T_c of cuprate superconductors so low (*1*)? The question stems from the fact that, knowing the natural energy scales in the high-T_c superconductors (such as the electron kinetic and potential energy), one would expect a much higher transition temperature than is observed experimentally. It is the pairing interactions between carriers that ultimately lead to the superconducting state. This superconducting state is stabilized by an energy gap. The stronger the pairing, the bigger the gap. Thus, more intense thermal fluctuations are required to destroy the superconducting state, and this means T_c is higher. For the cuprates as a class of high-T_c superconductors, the natural energy scales are much larger than the T_c, which is typically 50 to 100 K (or 0.005 to 0.01 eV). Moreover, researchers have discovered a "pseudogap," a gaplike feature in the particle energy spectrum that develops at temperatures substantially higher than T_c. This further establishes the notion that the pairing interaction, which is large, is not the limiting factor for T_c. The pseudogap has been identified so far for a certain range of carrier densities, the so-called underdoped regime. The large difference between natural energy scales in these materials and the T_c raises the question of whether there is a feature at lower energy that we have not yet identified that directly determines the transition temperature for these materials.

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There are a few clues on what this hidden T_c energy scale might be. One of the main properties of superconducting state is the formation of a phase coherent condensate capable of carrying electric current without dissipation. The fraction of particles participating in the condensate determines the superfluid density ρ_s. Thus, one clue comes from the so-called Uemura plot, which shows the direct proportionality between T_c and ρ_s (both experimentally measured quantities) in the underdoped regime, indicating that the energy scale is set by ρ_s (*2*).

Recently, new experimental findings have given more specific clues on the nature of the low-energy scale that determines the superconducting T_c. From inelastic neutron-scattering experiments, one finds a remarkably simple relation between T_c and the splitting of the incommensurate peaks or the peak (half) width δ near the antiferromagnetic wavevector (π,π) (*3*, *4*) [for explicitly observed incommensuration in YBCO123, see (*5*)]:

$$k_B T_c = \hbar v^* \delta \qquad (1)$$

where k_B is the Boltzmann constant and $\hbar$ is the Planck constant. This equation relates the energy scale $k_B T_c$ to the momentum scale δ, similar to the conventional $\omega = vk$ relation for excitation with energy ω and momentum k, propagating with some velocity v. On the basis of this very simple analogy, it was argued that the proportionality of T_c versus δ in fact implies very slow moving charge objects, whose phase coherence is responsible for the superconductivity. The characteristic velocity was found to be $\hbar v^* = 17$ meV-Å for underdoped LSCO and $\hbar v^* = 35$ meV-Å for YBCO123 (*4*), the two high-T_c compounds most studied by inelastic neutron scattering. Velocity v^* remains constant for the whole underdoped regime in both compounds. No theoretical assumptions are needed to extract v^* from Eq. 1. Any attempts to reconcile these values with the typical carrier velocity, called Fermi velocity (v_F), in high-T_c compounds fail. v^* values are about two orders of magnitude smaller than the Fermi velocity: $\hbar v_F \sim 1$ to 4 eV-Å from the band calculations or measured along $(0,0) \rightarrow (\pi,\pi)$ momentum direction (*6*, *7*). Simple estimates for the effective mass renormalization would yield the heavy charged excitations in the system with typical mass m^* relative to electron mass m: $v_F/v^* = m^*/m \sim 50$ to 100. The heavy charge mass m^* or, more precisely, the low charge mobility might be expected in these materials as a consequence of proximity to insulating state with no charge mobility.

The fact that small velocity enters into linear relation between T_c and inverse length scale δ (Eq. 1) implies that it is precisely these slow moving (heavy mass) objects that are responsible for the formation of the superconducting state. In contrast to the conventional description of superconductivity with electrons carrying the current without dissipation, Eq. 1 suggests that carriers of electricity

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