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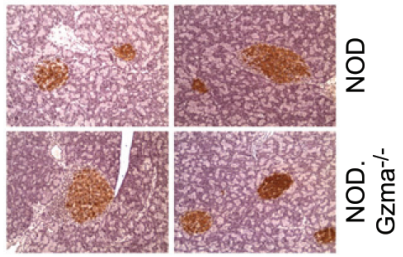
In This Issue of *Diabetes*

By Max Bingham, PhD

Granzyme A: Deficiency Breaks Immune Tolerance to Promote Autoimmune Diabetes

The role of granzyme A in the autoimmune component of type 1 diabetes is the focus of a study by Mollah et al. (**p. 3041**), who suggest that it may have a kind of housekeeping role in cells, cleaning up aberrant DNA and nucleic acid fragments. Crucially, however, they say that when it is not present at adequate levels (as seems to be the case in type 1 diabetes), the resulting leftover fragments fool the immune system and specifically type 1 interferons into thinking they might be viral in origin. When this occurs in pancreatic islets, β-cell destruction can be the result. The study focuses on NOD mice with a granzyme A deficiency. In a series of experiments, the authors attempt to delineate possible pathways relating to granzyme A and its potential to mediate autoimmune diabetes. In initial experiments they report that NOD mice lacking granzyme A developed higher rates of diabetes than controls and that they had higher levels of β-cell–specific $CD8^+$ T cells in islets, suggesting that the lack of granzyme A results in an autoimmune effect. Next, using NOD mice engineered to never develop diabetes, the authors found that introducing granzyme A deficiency resulted in about 30% of the population developing diabetes. With further analysis they say this likely demonstrates that the deficiency of granzyme A breaks immune tolerance that would otherwise protect the mice. Author Thomas W.H. Kay told *Diabetes*: "Our findings advance the understanding of the etiology of autoimmune diabetes for which no trigger has yet been identified, although viruses are under suspicion. The new insight here is that cytoplasmic nucleic acids can activate the innate immune system and trigger organ-specific autoimmune disease, most likely because they are mistaken for viral nucleic acid. We also link granzyme A to maintenance of immune tolerance, which was not recognized before."



Representative images of islets from 4-week-old wild-type NOD and NOD.Gzma$^{-/-}$ mice, stained with anti-insulin antibodies. Original magnification ×100.

Mollah et al. Granzyme A deficiency breaks immune tolerance and promotes autoimmune diabetes through a type 1 interferon–dependent pathway. Diabetes 2017;66:3041–3050

An Eye Test to Detect Cognitive Decline (and Alzheimer Disease) in Patients With Type 2 Diabetes

A simple 5-min eye test, using retinal microperimetry, might be able to identify mild cognitive impairment or even Alzheimer disease in patients with type 2 diabetes. As a result, Ciudin et al. (**p. 3098**) say that it should be possible to quickly screen patients in routine appointments for likely impairments and then to send them for more accurate, diagnostic evaluations. They compared groups of patients with type 2 diabetes with mild cognitive impairment, Alzheimer disease, or normal cognitive abilities ($n = 35$ per group). In parallel they also investigated smaller groups of individuals without type 2 diabetes but with similar levels of cognitive abilities. Each individual had a variety of psychological and biochemical tests, a series of MRI-based brain scans, and testing for retinal sensitivity via Macular Integrity Assessment retinal microperimetry. According to the authors, the patients with type 2 diabetes had the lowest retinal sensitivity when Alzheimer disease was present, less sensitivity with mild cognitive impairment, and normal sensitivity with normal cognitive abilities. Clear correlations with brain activity detected by MRI and positron-emission tomography approaches were also reportedly evident. In the parallel studies in individuals without diabetes, similar patterns were also apparent but were not statistically significant. The authors say this was likely due to a lack of power, which could be remedied with studies with larger sample sizes. They also suggest that after further study, retinal microperimetry could potentially be used as a test for cognitive decline in the general population. Author Rafael Simó said: "Our findings reveal that retinal microperimetry can be considered an effective and reliable tool for discriminating patients with Alzheimer disease from those with mild cognitive impairment or normal cognition. This is a relevant result because the identification of patients with prodromal stages of Alzheimer disease, such as the mild cognitive impairment, is precisely the target of campaigns for the early detection of Alzheimer disease."

Ciudin et al. Retinal microperimetry: a new tool for identifying patients with type 2 diabetes at risk of developing Alzheimer disease. Diabetes 2017;66:3098–3104

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Progressing From Autoimmunity to Type 1 Diabetes: TEDDY Cohort Update

Data from The Environmental Determinants of Diabetes in the Young (TEDDY) study suggest that factors affecting the risk of developing islet autoimmunity are different from factors that subsequently affect the risk of progression to type 1 diabetes once multiple autoantibodies are present. According to Krischer et al. (**p. 3122**), once multiple autoantibodies appear, the risk of progression did not appear to be affected by family history of type 1 diabetes. However, younger age and the timing of the initial appearance of multiple autoantibodies are thought to be linked to increased risk of progressing to type 1 diabetes. Additionally, the contribution of non-HLA gene polymorphisms to diabetes risk likely changes once autoantibodies appear. The analysis focuses on the TEDDY cohort, which is a prospective cohort of just over 8,500 children. Recruited at birth, the participants have undergone genetic screening for various high-risk genotypes previously associated with the risk of developing type 1 diabetes as well as regular prospective follow-up and assessments for islet autoantibodies. The authors report that by mid-2016, 412 children had developed multiple persistent autoantibodies and that just under half had progressed to type 1 diabetes. As well as reporting the likely impact of the various factors on progression to type 1 diabetes, they say that high-risk HLA haplotypes are likely not associated with the risk of type 1 diabetes through their contribution to the development of autoimmunity. Author Jeffrey P. Krischer commented: "TEDDY is helping us learn that type 1 diabetes is a heterogeneous disease even among those with high-risk genotypes. The stage of the disease and the age of the affected individual play an important role in defining what factors affect the rate of disease progression. These are the potential targets for intervention strategies seeking to alter progression, which now need to be customized to the individual. The TEDDY population is still quite young and these patterns may be altered as the population approaches puberty and beyond."

Krischer et al. The influence of type 1 diabetes genetic susceptibility regions, age, sex, and family history on the progression from multiple autoantibodies to type 1 diabetes: a TEDDY study report. Diabetes 2017;66:3122–3129

A Mechanism for β-Cell Destruction in Type 1 Diabetes: Interferons, STAT4, and Granzyme B

Type 1 interferons are likely central to the β-cell destruction and the loss of insulin production in type 1 diabetes. Despite some evidence for their involvement, the precise mechanisms have remained largely elusive until now. According to Newby et al. (**p. 3061**), it seems likely that type 1 interferons augment islet-infiltrating cytotoxic T lymphocytes ($CD8^+$ T cells) to rapidly gain function through the direct binding of phosphorylated STAT4 (pSTAT4) to the genetic promoter region of granzyme B. The experiments center on engineered human β-cell–specific cytotoxic T lymphocytes that have β-cell autoreactivity. At the core of the work is the subsequent exposure of the cells to type 1 interferons and their effects on primary human islets and β-cells. The authors report that the exposure of β-cells to the lymphocyte/interferon combination did indeed result in heightened β-cell lysis. Dosing experiments then largely confirmed the effect. Exploring the mechanisms, they say that expression levels of GZMB, the gene for granzyme B, were increased but that other potential cytotoxic factors (FasL and IFNγ) did not increase. Then, using various inhibitors, they go on to show that blocking granzyme B abolished β-cell lysis. Further experiments then implicated pSTAT4 binding to the promotor of GZMB, and the result was increased granzyme B protein levels and cell lysis. Author Clayton E. Mathews commented: "The role of type 1 interferons in the pathogenesis of autoimmune diabetes has received renewed attention recently. These cytokines are a critical link between genetic and environmental factors that promote type 1 diabetes, as type 1 interferons are produced in response to viruses and intracellular bacteria. Here we demonstrate that the final effector cells in type 1 diabetes, cytotoxic $CD8^+$ T cells, exhibit enhanced lytic potential when exposed to physiological levels of interferon α or β. These studies significantly bolster our understanding of immune factors that enhance β-cell death and point to type 1 diabetes as an interferonopathy."

Newby et al. Type 1 interferons potentiate human $CD8^+$ T-cell cytotoxicity through a STAT4- and granzyme B–dependent pathway. Diabetes 2017;66:3061–3071

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