much greater than that of short-lived soil microbes[4,15–17]. The authors suggest that the increased microbial activity observed in their study probably reflects the stimulatory effects of elevated temperatures associated with climate change.

There are, however, potential issues when drawing global inferences from the data analysed by Bond-Lamberty and co-workers. Most of the data came from spot measurements of soil-respiration rates that were obtained by many different researchers, who used a variety of methods to work out the contributions of soil microbes. This diversity of methods might have led those researchers to come to contrasting conclusions about the relative importance of soil microbes in their studies. Moreover, Bond-Lamberty *et al.* used simplifying assumptions to translate hourly or daily snapshots of respiration rates into annual fluxes of CO_2, but did not take into account the uncertainty in these calculations. The soil-respiration data set is also limited in its temporal coverage of individual sites: repeated observations were available for only a handful of sites, yet recurrent observations are necessary to prevent temporal trends from being obscured by factors that vary between sites.

The authors acknowledge and account for some of these limitations in their statistical analyses, but clearly there is room for a more rigorous investigation. This would require researchers to gather continuous time series of soil respiration and its component fluxes, and demands the use of precise methods for quantifying uncertainty and for extrapolating local measurements to determine trends in larger regions. Despite the limitations, Bond-Lamberty and colleagues' work is valuable because it aids our understanding of soil's long-term potential for sequestering carbon — as well as how this sequestration might be threatened by accelerated rates of organic-matter decomposition by soil microbes. Their findings will be crucial for developing and testing models of the global carbon budget, of which soil carbon is a central component.

Fluxes of CO_2 across whole ecosystems are often measured using eddy-covariance towers. By contrast, continuous measurements of soil respiration and decomposition by microbes are not broadly available for sites worldwide or do not cover multi-year periods. The establishment of long-term observational projects such as the US National Ecological Observatory Network (NEON), which monitors fluxes of soil CO_2 among other ecological measures, will create opportunities for the systematic evaluation of temporal trends and the underlying causes of changes in the rates at which CO_2 is lost from soil. Such data will be paramount for developing regional and global models of the carbon cycle, as well as for assessing climate change and the strategies by which it might be mitigated[18]. ■

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AUTOIMMUNITY

Peptide secretion triggers diabetes

An autoimmune attack on cells that make the hormone insulin causes type 1 diabetes. A mouse study reveals that pancreatic-cell release of insulin peptide fragments into the bloodstream triggers this harmful process. SEE LETTER P.107

JIAJIE WEI & JONATHAN W. YEWDELL

Diabetes arises from problems in the regulation of blood glucose, which is controlled by releasing the hormone insulin. The amount of insulin made is abnormally low in type 1 diabetes owing to the autoimmune-mediated destruction of insulin-producing β-cells in the pancreas. Wan *et al.*[1] reveal on page 107 how this immune attack is triggered.

Type 1 diabetes was a lethal condition with a life expectancy of just months until the discovery of insulin in 1921 enabled clinical management by insulin injection[2]. Although this therapy greatly extends life expectancy, a deeper understanding of the disease is needed to develop treatments that delay or prevent disease onset.

Studies of non-obese diabetic (NOD) mice, which spontaneously develop the disease, have provided insights into the mechanisms that cause the condition. Such work has revealed that T cells of the immune system have a key role in destroying insulin-producing pancreatic β-cells. T-cell immunosurveillance is aided by antigen-presenting cells, which present peptide fragments called antigens on their surface bound to major histocompatibility complex (MHC) class I and II molecules. T cells typically encounter antigen-presenting cells in the lymph nodes, and their T-cell receptor samples the antigens presented on MHC molecules. T cells that respond to self-antigens are normally eliminated as they mature in the thymus gland, but imperfections in this process can lead to autoimmunity. Although many proteins present in pancreatic β-cells could potentially provide the autoimmune trigger for type 1 diabetes, insulin is the culprit in NOD mice[2].

In type 1 diabetes in humans and NOD mice, the presentation of a peptide consisting of amino acids 12 to 20 of insulin's B chain (B:12–20) by MHC class II molecules can activate CD4 T cells that recognize this peptide[3]. In NOD mice, a class II MHC molecule called I-A^{g7} presents B:12–20 to CD4 T cells and activates them. These cells then initiate a process that activates CD8 T cells, which are specific for other β-cell peptides[4]. Activated CD8 cells kill β-cells, leading to diabetes when the T cells eliminate enough β-cells. The risk of a person developing type 1 diabetes is often linked to MHC class II genes, which are among the mostly highly variable human genes. The gene encoding the version of MHC class II called HLA-DQ8 is tightly associated with the disease[5]. Remarkably, HLA-DQ8 has a highly similar peptide-binding specificity to that of I-A^{g7} (ref. 6).

"Why isn't there selection against the generation of secreted insulin peptides that trigger autoimmunity in humans?"

Wan and colleagues confirmed the pathological potential of T cells that are specific for I-A^{g7}–B:12–20 complexes by introducing such T cells into NOD mice under conditions that generate enough CD4 T cells to cause type 1 diabetes. As a control, the authors did a similar transfer into NOD mice that have a

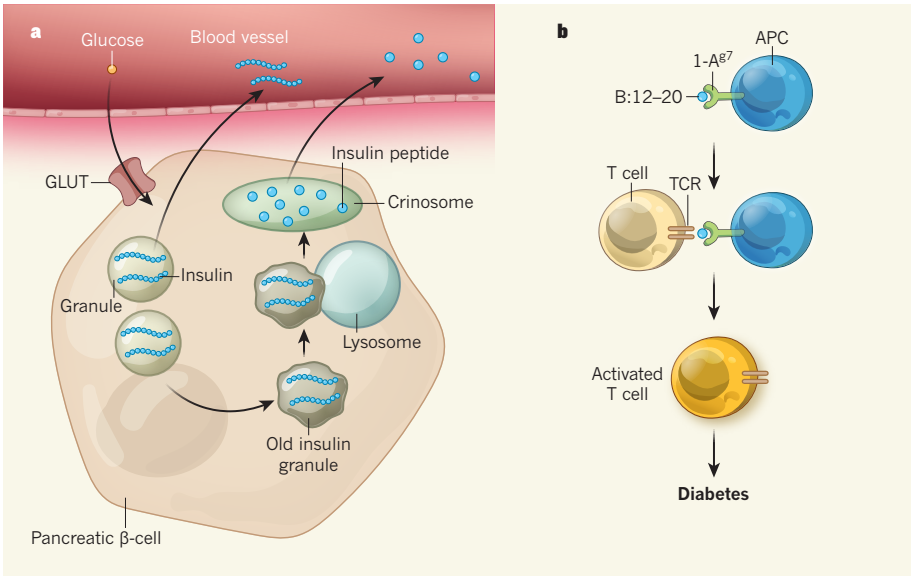

Figure 1 | Insulin and type 1 diabetes. If T cells launch an autoimmune attack on pancreatic β-cells, which produce insulin protein, it causes diabetes. The source of the specific insulin peptides that can prime the T cells that give rise to diabetes has remained unknown. **a**, Wan *et al.*[1] have now identified this source. Glucose from the blood enters β-cells through the GLUT channel protein, triggering the release of insulin from granules into the blood. The group found that old insulin granules are destroyed by fusing with an organelle called the lysosome to form another organelle known as the crinosome, in which insulin peptides arise. The peptides enter the bloodstream together with full-length insulin after glucose influx. **b**, The authors report that lymph nodes (not shown) are a site where an insulin peptide that might trigger diabetes (such as amino-acid residues 12 to 20 of the insulin B chain; B:12–20) can bind to a receptor termed I-A^{g7} on an antigen-presenting cell (APC) of the immune system. When such a peptide-bound APC encounters a T cell that recognizes the peptide through its T-cell receptor (TCR), this activates the T cell and sets in motion a process that can cause diabetes.

mutation in insulin that renders the antigen non-immunogenic. Several months later, the authors sequenced RNA from T cells derived from the transferred cells. These T cells expressed genes characteristic of an activated state only in the mice that had the immunogenic version of the antigen. Moreover, when these activated T cells were transferred into NOD mice that lacked T cells, they caused type 1 diabetes much more rapidly than when T cells from the control mice were used instead, confirming the role of these cells and this specific antigen in the generation of diabetes.

The authors sought to investigate how and where the diabetes-causing CD4 T cells are activated. They devised a highly sensitive and technically challenging microscopy approach that measures T-cell recognition of I-A^{g7}–B:12–20 complexes by monitoring a decrease in the mobility of CD4 T cells in mouse lymph nodes transferred from animals into a culture medium that promoted T-cell proliferation. This approach builds on previous findings that presentation of this antigen occurs in lymph nodes throughout the body, not just in those that drain from the pancreas[7]. Control experiments established that CD4 T cells are not activated by this antigen in NOD mice lacking I-A^{g7} or in animals that have an insulin mutation that prevents B:12–20 peptide binding to I-A^{g7}.

How do antigen-presenting cells in the lymph node acquire insulin peptides? One possibility is that they take up and process full-length insulin, given that these cells express insulin-binding receptors. However, when mice received a drug that blocks insulin binding and uptake, this did not block insulin recognition by CD4 T cells in lymph nodes.

So where are these insulin peptides generated? The authors turned their attention to pancreatic β-cells. These cells contain large amounts of insulin stored in granules, which are released into the bloodstream when blood glucose rises after a meal. As a quality-control measure, insulin has an 'expiration date', and old insulin granules are 'retired' and degraded in an organelle called a crinosome, which forms when a granule fuses with an organelle called a lysosome (Fig. 1).

By using a mass-spectrometry technique to identify peptides, Wan *et al.* found that crinosomes, but not insulin granules, contain substantial amounts of insulin peptides that are associated with diabetes. The authors determined that intravenously administered insulin peptides can rapidly reach antigen-presenting cells in lymph nodes, consistent with a model in which insulin peptides linked to diabetes are released into the bloodstream.

By providing an explanation of how disease-causing T cells can be activated, Wan and colleagues' findings raise many important questions. Given the short life expectancy for patients with untreated type 1 diabetes, one might have expected robust selection pressure against HLA-DQ8. Yet it is present at extremely high frequency in many ethnic groups[8], suggesting that there is a strong counterbalancing selective advantage in retaining HLA-DQ8. And why isn't there selection against the generation of secreted insulin peptides that trigger autoimmunity in humans? Perhaps the peptides have some positive functions, such as hormonal activity, that might also explain the timing of their release from β-cells together with insulin on glucose stimulation. It will be interesting to learn whether different types of secretory cell release peptides generated in crinosomes, and whether this contributes to other autoimmune diseases.

Wan *et al.* show that the activation of diabetes-causing T cells in NOD mice is independent of antigen presentation by B cells or dendritic cells. Which type of antigen-presenting cell is therefore responsible? Perhaps the most puzzling question of all is how insulin peptides activate T cells in the absence of the inflammatory signals that are usually needed to trigger an immune response. NOD mice are maintained in pathogen-free conditions, so they are unlikely to have infections that could provide the necessary inflammatory cues. Microorganisms that naturally reside in NOD mice could potentially provide immune triggers. Indeed, antibiotics can modulate type 1 diabetes susceptibility in NOD mice[9], implicating bacteria in disease pathogenesis.

Although insulin supplements can provide a profound improvement in diabetes treatment, the situation is far from perfect and the life expectancy of those who develop type 1 diabetes is decreased by more than a decade[10]. By uncovering key steps in the development of this condition, Wan and colleagues' findings might hasten the day when type 1 diabetes is relegated to medical history. ■

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