News & views

Immunology

A subset of T cells branded as seeds for type 1 diabetes

Stephen J. Turner & Nicole L. La Gruta

The identification of a specific subpopulation of immune-system T cells that drives type 1 diabetes provides insight into the development of autoimmune disease, and could point the way to new therapies. **See p.156**

A characteristic of many autoimmune diseases, including type 1 diabetes, is an immune response that persists and does not resolve. On page 156, Gearty *et al.*[1] pinpoint a specific group of T cells in the immune system that sustain this autoimmune response. The finding has implications for treatments that seek to modulate immune responses.

A hallmark of many immune responses is the generation of what are called effector responses, which provide targeted defence against infection. For example, a robust effector response against a viral infection is often mediated by immune cells called CD8 T cells. In such responses, which are typically transient, CD8 T cells become activated, then proliferate and differentiate into effector cells that can kill the virus-infected cells. Once the infection has been cleared, usually after one to two weeks, marking the end (resolution) of the defensive response, most of the effector T cells die. However, some persist, generating a population of memory T cells that can respond to the same threat if it is encountered again.

But situations can arise in which the target is not cleared, such as during chronic viral infection (Fig. 1a) or in cancer, and T cells are programmed to exist for a limited time, after which their activity is lost. This loss of immune-cell activity, known as T-cell exhaustion, is regulated through the expression (mediated by the transcription-factor protein TOX)[2] of inhibitory receptor proteins, such as PD1 and LAG3; these act as 'checkpoints' to suppress the effector function and proliferative potential of T cells[2–4].

Some autoimmune diseases, including type 1 diabetes, are driven by aberrant responses of CD8 T cells. Abnormal responses act both in targeting healthy tissues and in facilitating the diseases' remarkable persistence and lack of immune resolution. In type 1 diabetes, self-reactive CD8 T cells target and destroy β-cells in the pancreas (Fig. 1b) that produce the hormone insulin, resulting in abnormally high levels of sugar in the blood[5].

Using a well-characterized mouse model of type 1 diabetes, Gearty *et al.* followed the fate of CD8 T cells that specifically recognize a fragment (called an antigen) of the β-cell protein IGRP over the 5–30-week course of the disease. The authors monitored the cells in a body tissue called the pancreatic draining lymph node, where the cells are first activated by recognizing the IGRP antigen, and also in the pancreas, where they exert their autoimmune attack.

Gearty and colleagues found IGRP-specific CD8 T cells in the pancreatic lymph node and pancreas of mice as young as five weeks old. Interestingly, the characteristics of the population of CD8 T cells in the pancreatic lymph node differ from those of the CD8 T cells in the pancreas throughout the course of the disease. Hallmarks of these cells in the pancreatic lymph node included high expression of the transcription-factor protein TCF1 and low

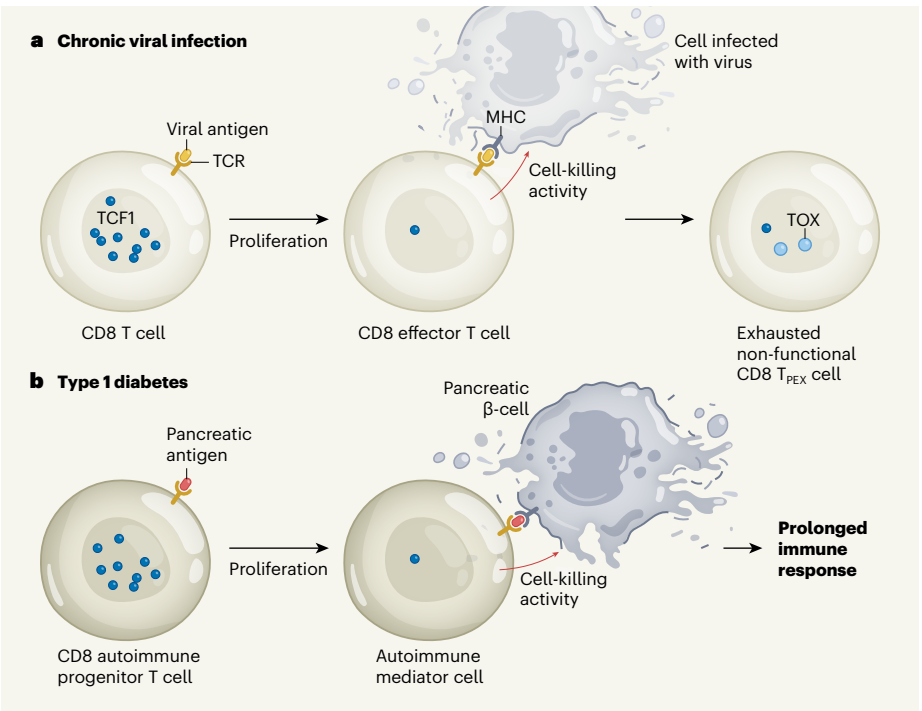

Figure 1 | Immune-cell populations differ in the duration of their defence response. a, Immune cells called CD8 T cells are involved in a short-term response to chronic viral infection. During this process, the cells' T-cell receptors (TCRs) recognize viral fragments (called antigens), and the cells initially have a high level of the transcription-factor protein TCF1. As they gear up to mount a defence, the cells proliferate and their TCF1 level falls. They become CD8 effector T cells, which kill infected cells that present the viral antigen on major histocompatibility complex (MHC) receptors. The immune cells soon enter a non-functional state called exhaustion, and are known as CD8 T_{PEX} cells, expressing the protein TOX. **b**, Gearty *et al.*[1] describe mouse experiments that examine how the autoimmune disease type 1 diabetes arises. The authors report that a subpopulation of CD8 T cells (autoimmune progenitor cells) gives rise to autoimmune mediator cells, which cause disease by killing pancreatic β-cells. Although this process initially mirrors aspects of defence against a chronic infection, for unknown reasons the T cells do not become exhausted.

expression of the proteins PD1 and CD39. By contrast, the IGRP-specific CD8 T cells in the pancreas exhibited more-differentiated characteristics — low levels of TCF1 and high levels of PD1 and CD39. TCF1 is essential for the establishment and long-term maintenance of memory CD8 T cells because it promotes cellular self-renewal[6,7].

Stem-cell-like populations expressing high levels of TCF1 have been observed during T-cell responses to acute infection, chronic infection and tumours[6,8–10]. Moreover, this population of T cells can self-renew and also 'seed' the more-differentiated effector T cells and the pool of memory cells. In these cases of chronic infection and cancer, programmed functional limits are applied to the differentiated effector cells, leading to T-cell exhaustion. Gearty and colleagues' findings show echoes of this pattern, establishing that the development of type 1 diabetes involves a differentiation process in which cells — called autoimmune progenitor cells — that have high levels of expression of TCF1 then transition into effector T cells, called autoimmune mediator CD8 T cells, with low levels of TCF1 expression. These cells are initially located in the pancreatic lymph node. They then move into the pancreas, where they differentiate further and target the pancreatic tissue, causing disease, a change probably driven by their activation through antigen recognition.

The authors showed that animals given autoimmune progenitor cells expressing high levels of TCF1 developed type 1 diabetes, whereas animals given autoimmune mediator cells that had low levels of TCF1 expression did not develop the condition (probably because these cells were unable to persist long enough to cause sustained tissue damage in the pancreas). The transferred autoimmune progenitor cells generated not only autoimmune mediator cells, but also a population of self-renewing autoimmune progenitor cells that expressed high levels of TCF1. When these newly generated autoimmune progenitor cells from diabetic mice were transferred to other animals, the recipient mice developed type 1 diabetes. Blocking the exit of β-cell-specific autoimmune mediator CD8 T cells from the pancreatic lymph node resulted in an eventual loss of disease-causing autoimmune mediator CD8 T cells in the pancreas. These data show that the autoimmune progenitor cells act as a self-sustaining reservoir in the pancreatic lymph node, and are the source of the disease-causing autoimmune mediators.

Notably, studies of other animal models that report a similar type of self-renewing T-cell progenitor population in the context of chronic antigen exposure (such as chronic infection and cancer) indicate that such cells exhibit signs of exhaustion; they are called precursors of exhausted T cells (T_{PEX} cells)[8,9,11]. Surprisingly however, despite the sustained response of CD8 T cells observed in type 1 diabetes, the autoimmune progenitor cells identified by Gearty *et al.*, expressing high levels of TCF1, retained their functionality. Moreover, the autoimmune mediator cells arising from this population were highly functional. Despite some higher than normal expression of inhibitory receptors, particularly for the cells in the pancreas, the autoimmune mediator cells expressed low levels of TOX, which is a key marker of exhausted CD8 T cells[2,4]. Analysis of the gene-expression profiles of the autoimmune progenitor cells revealed a transcriptional signature that is distinct from those of either conventional memory CD8 T cells or T_{PEX} cells.

Gearty and colleagues' study suggests that the mechanisms that help to limit CD8 T-cell responses in chronic infection and cancer do not apply in type 1 diabetes, or, at least, not in the animal model studied. Two major questions stemming from the study are whether this autoimmune progenitor population is a common driver of sustained autoimmune CD8 T-cell responses and, if so, why a program of exhaustion is not initiated in these cells under conditions of chronic exposure to the self-antigens that these cells recognize.

Answering these questions might aid efforts to develop new treatments to stem the tide of disease-mediating CD8 T cells. The authors suggest that a drug that could block the exit of such CD8 T cells from the pancreatic lymph node might be a promising therapy for type 1 diabetes. For this to be effective, however, treatment would need to start soon after initiation of the generation of CD8 T cells that can recognize the self-antigens. The molecular signature of the autoimmune progenitor cells, being so different from those of conventional memory T cells and T_{PEX} cells, might allow the cells to be selectively eliminated or an exhaustion program to be induced in them, halting the disease-causing immune response. On the flip side, understanding how these autoimmune progenitor cells evade the exhaustion program might offer insights that could be used in developing sustained, antigen-specific responses to cancer.

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Condensed-matter physics

Lost magnetism pinned on atomic rotations

Georg Woltersdorf

Crystal-lattice vibrations reveal the mechanism by which laser pulses can strip a metal of its magnetism. The vibrations absorb the angular momentum of electrons in a sample, allowing it to demagnetize. **See p.73**

More than two decades ago, physicists noticed a curious thing about thin magnetic films of nickel: their magnetization was reduced almost immediately when the metal was hit with extremely short, intense pulses of light[1]. In general, materials are magnetic when the intrinsic angular momentum (or spin) of each electron aligns parallel to that of its neighbours. Because electrons carry an electric charge, this angular momentum gives rise to a magnetic moment similar to the one that arises when an electric current flows through a wire loop. So when the nickel demagnetized rapidly, researchers were understandably puzzled about what happened to the angular momentum. Writing on page 73, Tauchert *et al.*[2] have found the answer to this long-standing question, showing that the vibrational modes of nickel's crystal lattice carry a large fraction of the lost angular momentum.

Since the original report that nickel could be demagnetized with light, several experiments