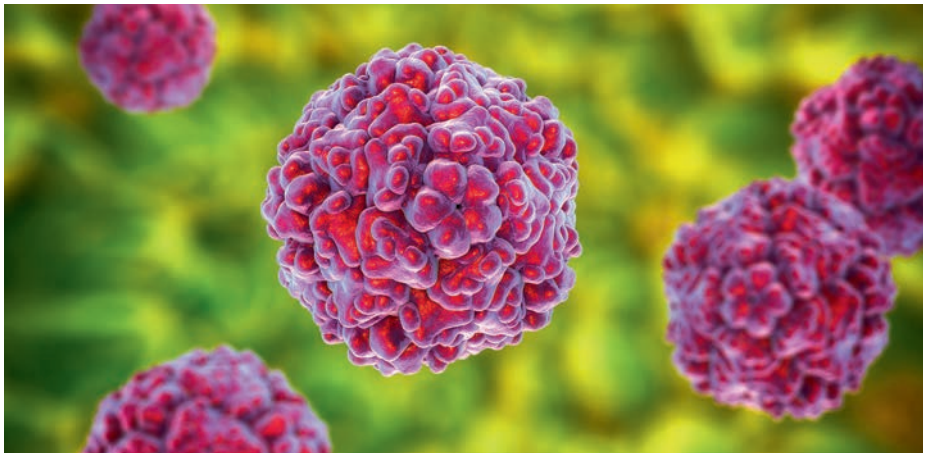
Milestone 23

An infectious cause for T1D?



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The development of type 1 diabetes (T1D) depends on a complex interplay between genetic factors (Milestone 3) and environmental factors that ultimately result in the autoimmune destruction of pancreatic β-cells (Milestones 7 and 8). Viruses have long been prime suspects as environmental triggers of T1D (particularly in the young), with the first investigators drawing on early epidemiological studies showing that disease incidence has a seasonal pattern and increases after enterovirus epidemics, and subsequent work showing that certain enteroviruses can infect β-cells and have a causative role in animal studies. It was the isolation of the enterovirus coxsackie virus B4 in 1979 from a 10-year-old boy who died as a result of T1D following a flu-like illness that drove the search for a viral aetiology of T1D (Yoon et al., 1979). Importantly, the isolated virus could cause hyperglycaemia following inoculation of mice. Forty years later, with the arrival of improved, more sensitive, sequencing technologies, Vehik et al. provided tantalizing evidence that prolonged enteroviral infection is a precursor to the development of autoimmune diabetes in young children.

Over the years, various mechanisms have been evoked to explain the link between viruses and autoimmune disease, including molecular mimicry and indirect immune activation. As evidence to support molecular mimicry, Atkinson et al. (1994) described a major T cell epitope of the β-cell enzyme glutamate decarboxylase recognized by individuals with T1D that has significant sequence similarity to a coxsackie viral peptide. By contrast, Horwitz et al. (1998) provided evidence suggesting instead that diabetes induced by coxsackie virus infection results from local inflammation, tissue damage and release of islet antigens that stimulate autoreactive T cells. A later study did not observe destructive islet inflammation following β-cell infection and instead linked infection to β-cell dysfunction and natural killer cell-mediated insulitis (Dotta et al., 2007). The exact mechanisms of potential viral causality or contribution to T1D are still a matter of debate.

"prolonged enteroviral infection is a precursor to the development of autoimmune diabetes in young children"

The report by Vehik et al. was one of a series of papers stemming from The Environmental Determinants of Diabetes in the Young (TEDDY) study — the largest multicentre prospective study of young children with a genetic susceptibility to T1D that aims to identify the environmental causes of T1D. Vehik et al. performed meta-genomic sequencing of monthly stool samples collected from newborn babies until detection of islet autoimmunity or T1D along with controls. They identified enterovirus B as the only virus in the human virome with a significant association with islet autoimmunity. Although the frequencies of enterovirus B infection did not differ between cases and controls, children with prolonged shedding of enterovirus B were more likely to develop islet autoimmunity. By contrast, human mastadenovirus C infection early in life was less frequent in children who developed islet autoimmunity than in those who did not, suggesting a protective effect. Finally, identification of an association between polymorphisms in the coxsackie virus and adenovirus receptor gene and susceptibility to T1D led the authors to propose that competition for receptor binding between adenovirus and coxsackie virus confers the protective effect of adenovirus. It is important to note that this study was limited to very young children, who account for only 10–20% of total new cases of T1D worldwide, and evidence that enterovirus B causes direct β-cell destruction is still lacking.

The TEDDY study also allowed the first extensive characterization of the gut microbiome in relation to T1D. A report by Vatanen et al. (2018) showed that the microbiomes of control children were enriched for genes related to fermentation and biosynthesis of short-chain fatty acids (SCFAs) compared with children with T1D, suggesting a protective effect of SCFAs. Moreover, the TEDDY cohort has provided insight into early colonization of the gut microbiome and the impact of breastfeeding, birth mode and other factors, as described in a companion paper (Stewart et al., 2018). Although only subtle compositional differences were observed between T1D cases and controls and cause or effect could not be discriminated, higher levels of *Streptococcus* sp. and *Lactococcus* sp. and lower levels of *Akkermansia* sp. in infants at risk of T1D provide further hints for the involvement of an altered microbiome in the development of T1D. Placing viral infection at the forefront of T1D aetiology has spurred current approaches that target viral infection to prevent islet autoimmunity.

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Milestone study
Vehik, K. et al. Prospective virome analyses in young children at increased genetic risk for type 1 diabetes. *Nat. Med.* **25**, 1865–1872 (2019)

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