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Current Opinion in Pharmacology

Enteroviral infections in the pathogenesis of type 1 diabetes: new insights for therapeutic intervention

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The development of islet autoimmunity and type 1 diabetes has long been linked with enteroviral infection but a causal relationship has proven hard to establish. This is partly because much of the epidemiological evidence derives from studies of neutralising antibody generation in blood samples while less attention has been paid to the pancreatic beta cell as a site of infection. Nevertheless, recent studies have revealed that beta cells express specific enteroviral receptors and that they can sustain a productive enteroviral infection. Importantly, they can also mount antiviral responses which attenuate viral replication and may favour the establishment of a persistent enteroviral infection. Together, these responses combine to create the Trojan horse by which enteroviruses might precipitate islet autoimmunity.

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Current Opinion in Pharmacology 2018, **43**:11–19

This review comes from a themed issue on **Endocrine & metabolic diseases**

Edited by **James Bowe** and **Shanta Persaud**

https://doi.org/10.1016/j.coph.2018.07.006

Type 1 diabetes (T1D) is characterised by the selective loss of insulin producing beta cells from the islets of Langerhans in the pancreas, meaning that affected individuals must administer exogenous insulin throughout their lives. The incidence of the disease is increasing [1] and although previously considered to be predominantly a disease of the young, it is now known to develop in all decades of life [2••]. As a consequence, there are likely to be significant numbers of older individuals with T1D who have been mis-diagnosed with Type 2 diabetes (T2D). These two observations suggest that the number of people affected by T1D may be larger than previously thought.

Type 1 diabetes arises from a complex interaction between genetic, immune and environmental factors which, as emphasized in comprehensive recent reviews [3,4] are poorly understood. In particular, the environmental influences have proven hard to identify, although studies as far back as the 1960s have implicated viral infection, particularly by human enteroviruses (HEV; single-stranded RNA (+) viruses from the picornavirus family), as a potentially important factor both in the triggering of islet autoimmunity and the onset of clinical disease. In support of this, a 2011 meta-analysis of 26 earlier studies provided evidence that enteroviral infection occurred 3.7 times more commonly in individuals with islet autoimmunity and was 9.8 times more likely at disease onset when compared to matched controls [5]. Since that time, additional studies have emerged to support this hypothesis [6]. In particular, evidence that enterovirus infections are more frequent prior to the appearance of islet autoantibodies has been found in several large prospective cohort studies [7–10]. Importantly, recent studies of unique pancreas biopsy samples from Norwegian patients with T1D (the DiViD samples [11]) have provided strong evidence for both the presence of HEV and enhanced islet anti-viral responses in newly-diagnosed patients [12,13•,14•,15]. In addition, ever more sensitive technologies are being developed to detect or interrogate viral infection and anti-viral responses in blood [8,16••,17–20], islets [12,21•,22•], stool [9] and other tissues [23–31]. These are currently being applied in new collaborative studies involving multiple laboratories who are employing differing expertise and complementary technologies to examine blinded tissue samples available from the network of Pancreatic Organ Donors with Diabetes (nPOD). The first results are due for publication soon and are expected to provide additional support for the enteroviral hypothesis in T1D.

Enteroviruses and beta cells: an unfortunate conjunction

Human beta cells are known to be susceptible to infection with HEVs, particularly members of the Coxsackievirus B family. Thus, isolated human islets can be productively infected with a range of different EV-B family members (CVBs and Echoviruses, many of which have been associated with T1D; Table 1) *in vitro*. Furthermore, among the various islet cells, it is the beta cells that are preferentially susceptible to infection [32–34], and this leads to a dramatic decrement in glucose-induced insulin secretion [21•,35••,36]. Tropism of HEVs for the islets has also been demonstrated *in vivo* in the pancreata of neonates who died following a lethal CVB infection [6,34,37] and in

Table 1

Examples of enterovirus serotypes associated with Type 1 diabetes or which have the ability to infect human islets *in vitro*

	Reference
General EV	[9,12,18,82–88]
CVB1-6	[7,8,32,33,35••,38,39,89–96]
Echovirus 3, 4, 6, 9, 16, 30	[91,97–107]
Coxsackie A	[107]

the pancreas of individuals with T1D [38,39]. This then raises the question: 'so why the beta cells?'

The tropism of enteroviruses for the beta cell is likely to be driven by at least two factors; first, these cells express receptors necessary for the binding and subsequent internalisation of the virus and secondly, they contain specific host factors which the virus can hijack to facilitate successful infection, replication and, perhaps, persistence. This latter point is interesting since the traditional view states that enteroviruses are not likely to establish persistent infections and this concept will be explored further below. The various potential receptors utilised by enteroviruses and their expression in human islets are summarised in Table 2 but one that is receiving particular attention is the Coxsackie and Adenovirus Receptor (CAR). This molecule is utilised as an entry vehicle by many of the viruses that are associated with T1D in epidemiological studies and, very recently, we have shown that a specific isoform of CAR, having a unique C-terminal PDZ binding domain (CAR-SIV) is selectively and highly expressed within the beta cell [40••]. Studies by Ylipaasto *et al.* have also demonstrated that infection of human islets with CVB4 and CVB5 was effectively prevented in the presence of an antibody that blocks CAR [41]. Intriguingly, in our work, the subcellular localisation of CAR-SIV was unusual in that it was not present primarily at the plasma membrane of beta cells, as might be expected, but rather it was located mainly in insulin secretory granules. This unexpected localisation implies that the virus could selectively enter the beta cell by a Trojan horse mechanism in which secretory granule proteins are hijacked as they emerge onto the cell surface during exocytosis, such that virus particles are then internalized by the endocytic machinery during membrane recovery (Figure 1). In support of this, electron microscopy studies by Frisk *et al.* of human islets infected with CVBs clearly show the presence of viral replication complexes and newly synthesised virions at, or near, insulin granule membranes [35••].

In recent years, a series of critical host factors required for successful HEV infections have been identified. These include PLA2G16 [42••] which is essential for virion-mediated genome delivery into the cytoplasm; phosphatidylinositol-4-kinase IIIβ (PI4KIIIβ) and its product phosphatidylinositol-4-phosphate (PI4P), which are critical for the generation of specialised organelles required for efficient viral replication [43,44]); polypyrimidine tract-binding protein 1 (PTBP1), which is utilized by the virus to promote cap-independent translation of viral RNA [36] and heat shock protein 90 (HSP90), which is

Table 2

Relevant enteroviral receptors and their expression in human beta cells/islets

Potential Enterovirus receptors and *role* [78]	Enteroviruses that utilise these receptors	Transcriptomic data suggesting expression in beta cells[a]	Protein expression in islets[b]
CAR *Uncoating*	Coxsackievirus B1-6	+++	+++ [40••]
DAF (CD55) *Attachment*	Coxsackievirus A21, B1, B3 & B5 Echovirus 3, 6, 7, 11–13, 20, 21, 25, 29, 30	++	HPA — not detected; [41]
ICAM1 *Uncoating*	Coxsackievirus A13, A18, A21 Rhinovirus Major group (91 serotypes)	Low	HPA — not detected in healthy controls; some evidence of upregulation in inflamed T1D islets [108]
ICAM5 *Uncoating*	Enterovirus D68	Negative	HPA — not detected
SCARB2 *Uncoating*	Enterovirus 71 Coxsackievirus A16	+++	HPA — ++
PSGL1 *Attachment*	Enterovirus 71 Coxsackievirus A16	Negative	HPA — not detected
α2β1 (VLA2) *Attachment*	Echovirus 1, 8	*ITGA2* — negative *ITGB1* — +++	HPA — not detected
α5β3 *Attachment*	Coxsackievirus A9, Echovirus 1, 9	*ITGA5* — negative *ITGB3* — negative	HPA — not detected + in isolated islets [41]

CAR, Coxsackie and adenovirus receptor; DAF, complement decay accelerating factor; ICAM1, intercellular adhesion molelcule-1; SCARB2, scavenger receptor class B member 2; PSGL1, P-selectin glycoprotein ligand 1; VLA2, very late antigen 2.

[a] *Source*: Transcriptomics of human islets. http://sandberg.cmb.ki.se/pancreas/.

[b] *Source*: Human Protein Atlas (HPA) or references. https://www.proteinatlas.org/.