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COMMENTARY

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Anti-viral innate immunity: Is it where type 1 diabetes really begins?

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Type 1 diabetes (T1D) is a common multifactorial autoimmune disease resulting from the destruction of insulin-producing β-cells in the pancreas as a consequence of dysregulated immune responses.[1] In the past few years, there has been a flurry of discoveries and advancements in our understanding of the immunopathogenic mechanisms at the basis of T1D development and progression. Despite genetic predisposition to T1D being considered a key risk factor, exogenous agents are now extensively thought to be responsible for the recent increase in the disease.[1] Accumulating evidence strongly supports the role of viral infections in the pathogenesis of autoimmune diabetes as one of the initial determinants that trigger β-cell destruction by autoreactive T lymphocytes.[1,2] In particular, the coxsackievirus B (CVB) is increasingly recognized as a smoking gun for T1D development.[1] While research studies point to a role of the adaptive immune response in T1D pathogenesis, with the prevalent view that cytotoxic T cells are directly involved in the tissue damage, there is growing appreciation that innate immunity is critical for initiating the early events leading up to the autoimmune process upon viral infections.[3,4] Innate immune cells physiologically reside in the endocrine pancreas where they recognise pathogens and give rise to the sequel of primary immune responses to warrant microbial clearance and tissue homoeostasis.[5] Nevertheless, it is possible that defects in sensing viruses, associated with impaired host immune responses, trigger β-cell autoimmunity in genetically susceptible individuals. In support of this concept, a recent study by Pedersen and co-workers revealed that single-nucleotide polymorphisms in genes of the innate anti-viral immune system are associated with T1D onset.[6] In particular, these researchers observed that multiple IFN-stimulated genes, such as the 2′-5′ oligoadenylate synthetase family of genes, are elevated in new-onset T1D, thus might cause inflammation in the islets and progression to diabetes.[6] In this context, it is possible to hypothesise that persistent pancreatic infections by T1D-related viruses could burst the innate cell responses, promoting the activation of self-reactive T lymphocytes, which in turn initiate or accelerate disease progression.

The innate immune system encompasses different cellular components, including dendritic cells (DCs), macrophages, and natural killer (NK) cells, that accumulate in the pancreas during the progressive phases of T1D[5] (Figure 1). Herein, conventional dendritic cells display a pivotal role in inducing T1D upon pathogen infections as these cells can capture and present β-cell-derived proteins and/or viral antigens, initiating the diabetogenic T cell-specific immune response[7] (Figure 1). Although plasmacytoid DCs (pDCs) have a low antigen-presenting capability,[8] they also participate in T1D development; indeed, pDCs detect viral RNA or DNA through Toll-like receptors (TLRs) and secrete huge amounts of interleukin (IL)-12, interferon (IFN)-α, and chemokines, sustaining the inflammatory microenvironment in the pancreatic tissue.[8] More specifically, experimental evidence showed that infection by CVB4 stimulated pDCs to produce IFN-α by engaging intracellular binding TLR7, which favours the differentiation of IFN-γ-producing $CD4^+$ T helper (Th)1 cells in T1D subjects[9] (Figure 1).

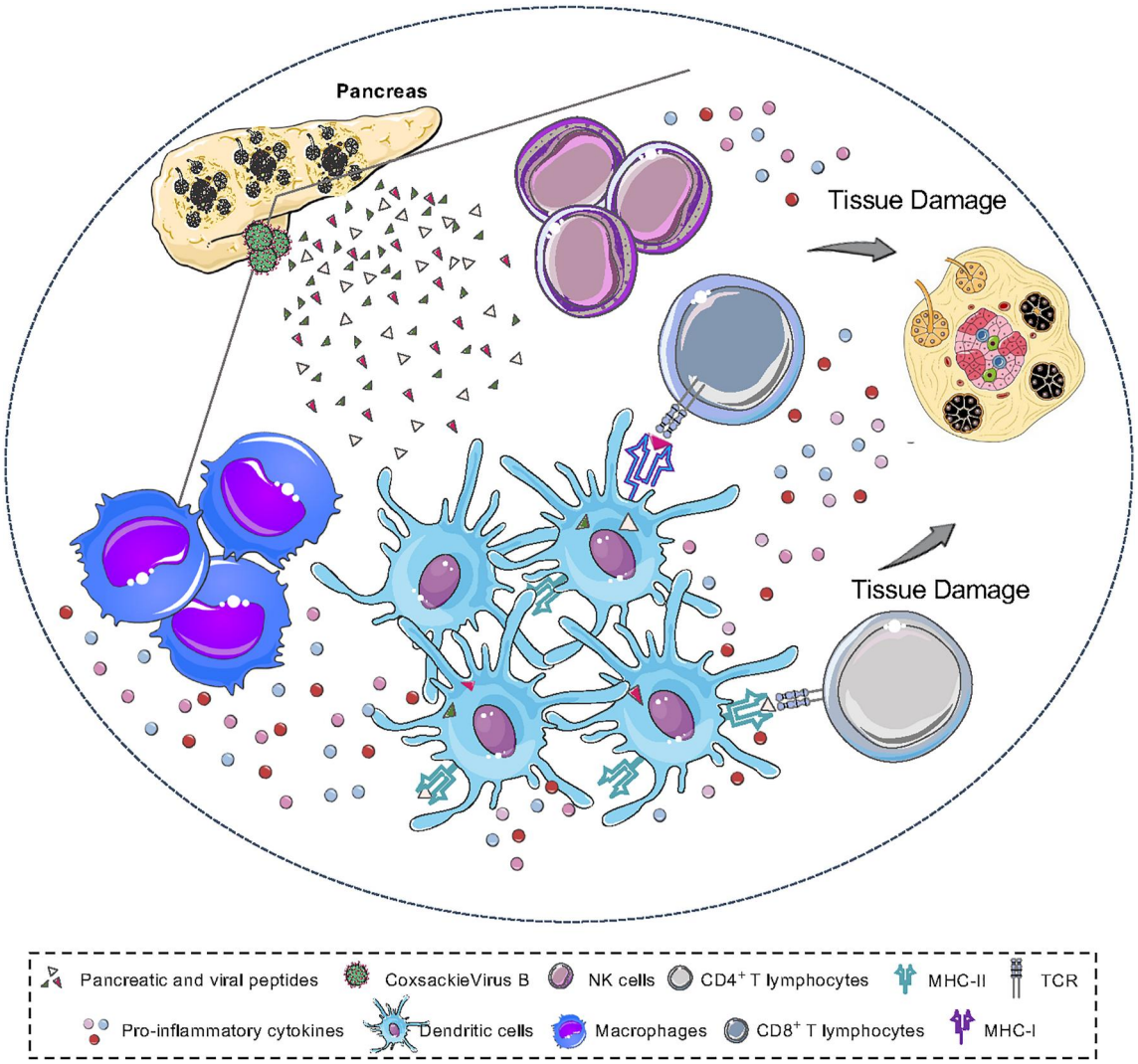

FIGURE 1 Schematic representation of the pathogenic interplay among viral infection, innate immune cell response and T cells in type 1 diabetes (T1D). Upon infection by coxsackievirus B4 in pancreatic tissue, the innate cells (i.e., macrophages, dendritic cells [DCs], and natural killer [NK] cells) activate the anti-viral immune response by producing several pro-inflammatory cytokines and direct kill the infected cells. DCs present β-cell-derived proteins and/or viral antigens to autoreactive T cells. MHC, Major Histocompatibility Complex; TCR, T Cell Receptor.

Pioneering studies in a non-obese diabetic mouse model have demonstrated that macrophages also strongly contribute to the establishment of a pro-inflammatory microenvironment, which sustains the activation of islet-specific autoreactive T lymphocytes[10] (Figure 1). As a relevant example, upon CVB4 infection, β-cells upregulated the surface markers of cellular stress (e.g., death receptor 4) and are engulfed by resident macrophages, with consequent production of pro-inflammatory cytokines and the presentation of pancreatic self-antigens[11] (Figure 1). An additional mechanism through which macrophages contribute to T1D development includes the production of IL-1β, tumour necrosis factor (TNF)-α, and reactive oxidation species, which directly destroy virus-infected β-cells with the subsequent spread of intracellular epitopes.[12,13] These cytokines, together with type I IFNs, classically known for interfering with the viral infection, have been implicated in the early stages of T1D autoimmunity by further enhancing IL-1β and IL-18 production by macrophages.[5] In this regard, recent experimental evidence revealed that in vivo inactivation and/or deletion of the type I IFN pathway in macrophages can prevent T1D onset,[14] supporting the key pathogenic role of this innate immune pathway in T1D development.

Other crucial players of the innate immune system influencing T1D pathogenesis are NK cells, the main lymphocyte subset that confers early protection against viruses, by killing infected cells. Indeed, it has been shown that autoimmunity against pancreatic islets can also originate from the direct cytolytic activity of NK cells towards β-cells persistently infected with CVB4[15] (Figure 1). Furthermore, β-cell apoptosis mediated by NK cells leads to epitope spreading, which together with IFN-γ production triggers the activation of self-reactive T cells.[15] Notably, additional studies have reported a low frequency of

NK cells, aberrant signalling of their activation receptor NKG2D and impaired cytolytic activity, especially towards pancreatic β-cells persistently infected with CVB4.[15] As a hypothesis, defective cytotoxicity of NK cells towards CVB4-infected cells might contribute to the persistence of the virus, thus triggering T1D development.[15]

In this Commentary, we highlighted the importance of the interplay between innate immunity and viral infections as a key piece in the complex puzzle of T1D etiopathogenesis. The biological relevance of the proposed model is reinforced by several findings and observations suggesting an increased rate of T1D during the recent COVID-19 pandemic due to the SARS-CoV-2 infection.[16,17] Consistently, the findings by Kendall and colleagues revealed a high risk of T1D development among infected subjects with SARS-CoV-2, especially at 1, 3, and 6 months after COVID-19.[18] Although no studies have investigated at the mechanistic level the impact of SARS-CoV-2 on innate immune cell functions in T1D, it is reasonable to hypothesise that altered inflammatory/innate responses contribute either directly or indirectly to pancreatic damage and subsequent autoimmune diabetes development.

Nowadays, researchers have explored many aspects concerning the pathogenic link between infection and anti-viral innate immunity in T1D; however, one of the key questions that remain to be addressed is why in some individuals the innate immune cell responses are inefficient in maintaining pancreatic immune homoeostasis. Possible explanations could rely on several inter-individual differences, such as (i) the presence of genetic susceptibility HLA haplotypes, (ii) expression of specific immune-related gene signatures (i.e., *IFN*, *IFIH1*, and *TYK2*),[4] and (iii) the altered crosstalk between innate immune cells and infiltrated autoreactive T lymphocytes.

Knowledge of the mechanisms and consequences of virus persistence in the initiation and progression of T1D may open perspectives for developing pharmacological approaches that target innate immune responses or viruses to halt T1D. In this scenario, clinical trials targeting innate immunity in T1D individuals have been carried out in the last few years; these include anti-IL-1 (i.e., Canakinumab, Anakinra, Gevokizumab, or Rilonacept),[19–21] anti-TNF-α (i.e., Etanercept),[22] and anti-IL-8 receptor (i.e., Ladarixin)[23] treatment. Nevertheless, limited effectiveness of these molecules against β-cell mass decline has been observed, although short-term transient inhibition of the IL-8 receptors improved metabolic control (i.e., HbA1c).[23] It is possible that at the time of the clinical intervention (i.e., T1D onset), aberrant innate immune cells have already triggered specific anti-pancreatic adaptive immune responses. Nonetheless, heterogeneity in the disease pathogenesis, also due to different T1D patient endotypes,[24] may represent a major barrier to therapeutic efforts. Thus, it is reasonable to hypothesise that an early intervention direct on innate immunity in autoantibody-positive at-risk subjects or specific vaccination against the major T1D-associated virus could be helpful to control the disease development.

The requirement for an efficient line of attack against T1D development is growing; therefore, it is essential to revisit and explore new approaches beyond the current concepts. Indeed, anti-viral strategies are now under investigation to prevent or clear persistent CVB infection[25,26] with a view to halting T1D development; however, they are still in the experimental phase or clinical trials. Overall, preventing the altered anti-viral innate immune response through specific vaccines and drugs might open new frontiers of therapy to control and/or prevent autoimmune diabetes and would be definitive proof of their causal role in triggering T1D.

AUTHOR CONTRIBUTIONS

All the authors contributed substantively to the design, writing, and editing of the commentary and approved the final version submitted for publication.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

Not relevant.

DATA AVAILABILITY STATEMENT

Data used in the paper can be found in the bibliography of the paper and are available in PubMed.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/dmrr.3623.

REFERENCES

1. Hober D, Sauter P. Pathogenesis of type 1 diabetes mellitus: interplay between enterovirus and host. *Nat Rev Endocrinol*. 2010;6(5):279-289. https://doi.org/10.1038/nrendo.2010.27
2. Jun HS, Yoon JW. A new look at viruses in type 1 diabetes. *Diabetes Metab Res Rev*. 2003;19(1):8-31. https://doi.org/10.1002/dmrr.337
3. Citro A, Campo F, Dugnani E, Piemonti L. Innate immunity mediated inflammation and beta cell function: neighbors or enemies? *Front Endocrinol (Lausanne)*. 2020;11:606332. https://doi.org/10.3389/fendo.2020.606332
4. Alidjinou EK, Hober D. Enteroviruses and type 1 diabetes: candidate genes linked with innate immune response. *EBioMedicine*. 2015;2(7):636-637. https://doi.org/10.1016/j.ebiom.2015.06.001
5. Zirpel H, Roep BO. Islet-resident dendritic cells and macrophages in type 1 diabetes: in search of Bigfoot's print. *Front Endocrinol (Lausanne)*. 2021;12:666795. https://doi.org/10.3389/fendo.2021.666795

6. Pedersen K, Haupt-Jorgensen M, Krogvold L, et al. Genetic predisposition in the 2'-5'A pathway in the development of type 1 diabetes: potential contribution to dysregulation of innate antiviral immunity. *Diabetologia*. 2021;64(8):1805-1815. https://doi.org/10.1007/s00125-021-05469-5
7. Marleau AM, Summers KL, Singh B. Differential contributions of APC subsets to T cell activation in nonobese diabetic mice. *J Immunol*. 2008;180(8):5235-5249. https://doi.org/10.4049/jimmunol.180.8.5235
8. Lande R, Gilliet M. Plasmacytoid dendritic cells: key players in the initiation and regulation of immune responses. *Ann N Y Acad Sci*. 2010;1183(1):89-103. https://doi.org/10.1111/j.1749-6632.2009.05152.x
9. Xia CQ, Peng R, Chernatynskaya AV, et al. Increased IFN-alpha-producing plasmacytoid dendritic cells (pDCs) in human Th1-mediated type 1 diabetes: pDCs augment Th1 responses through IFN-alpha production. *J Immunol*. 2014;193(3):1024-1034. https://doi.org/10.4049/jimmunol.1303230
10. Jun HS, Yoon CS, Zbytnuik L, van Rooijen N, Yoon JW. The role of macrophages in T cell-mediated autoimmune diabetes in nonobese diabetic mice. *J Exp Med*. 1999;189(2):347-358. https://doi.org/10.1084/jem.189.2.347
11. Horwitz MS, Ilic A, Fine C, Balasa B, Sarvetnick N. Coxsackieviral-mediated diabetes: induction requires antigen-presenting cells and is accompanied by phagocytosis of beta cells. *Clin Immunol*. 2004;110(2):134-144. https://doi.org/10.1016/j.clim.2003.09.014
12. Pukel C, Baquerizo H, Rabinovitch A. Destruction of rat islet cell monolayers by cytokines. Synergistic interactions of interferon-gamma, tumor necrosis factor, lymphotoxin, and interleukin 1. *Diabetes*. 1988;37(1):133-136. https://doi.org/10.2337/diabetes.37.1.133
13. Lee YS, Li N, Shin S, Jun HS. Role of nitric oxide in the pathogenesis of encephalomyocarditis virus-induced diabetes in mice. *J Virol*. 2009;83(16):8004-8011. https://doi.org/10.1128/jvi.00205-09
14. Marro BS, Legrain S, Ware BC, Oldstone MB. Macrophage IFN-I signaling promotes autoreactive T cell infiltration into islets in type 1 diabetes model. *JCI Insight*. 2019;4(2). https://doi.org/10.1172/jci.insight.125067
15. Nekoua MP, Alidjinou EK, Hober D. Persistent coxsackievirus B infection and pathogenesis of type 1 diabetes mellitus. *Nat Rev Endocrinol*. 2022;18(8):503-516. https://doi.org/10.1038/s41574-022-00688-1
16. Gottesman BL, Yu J, Tanaka C, Longhurst CA, Kim JJ. Incidence of new-onset type 1 diabetes among US children during the COVID-19 global pandemic. *JAMA Pediatr*. 2022;176(4):414-415. https://doi.org/10.1001/jamapediatrics.2021.5801
17. Montefusco L, Bolla AM, Fiorina P. Should we expect a wave of type 1 diabetes following SARS-CoV-2 pandemic? *Diabetes Metab Res Rev*. 2022;38(4):e3529. https://doi.org/10.1002/dmrr.3529
18. Kendall EK, Olaker VR, Kaelber DC, Xu R, Davis PB. Association of SARS-CoV-2 Infection with new-onset type 1 diabetes among pediatric patients from 2020 to 2021. *JAMA Netw Open*. 2022;5(9):e2233014. https://doi.org/10.1001/jamanetworkopen.2022.33014
19. Moran A, Bundy B, Becker DJ, et al. Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicentre, randomised, double-blind, placebo-controlled trials. *Lancet*. 2013;381(9881):1905-1915. https://doi.org/10.1016/s0140-6736(13)60023-9
20. Seelig E, Timper K, Falconnier C, et al. Interleukin-1 antagonism in type 1 diabetes of long duration. *Diabetes Metab*. 2016;42(6):453-456. https://doi.org/10.1016/j.diabet.2016.08.005
21. White PC, Adhikari S, Grishman EK, Sumpter KM. A phase I study of anti-inflammatory therapy with rilonacept in adolescents and adults with type 1 diabetes mellitus. *Pediatr Diabetes*. 2018;19(4):788-793. https://doi.org/10.1111/pedi.12634
22. Mastrandrea L, Yu J, Behrens T, et al. Etanercept treatment in children with new-onset type 1 diabetes: pilot randomized, placebo-controlled, double-blind study. *Diabetes Care*. 2009;32(7):1244-1249. https://doi.org/10.2337/dc09-1571
23. Piemonti L, Keymeulen B, Gillard P, et al. Ladarixin, an inhibitor of the interleukin-8 receptors CXCR1 and CXCR2, in new-onset type 1 diabetes: a multicentre, randomized, double-blind, placebo-con trolled trial. *Diabetes Obes Metab*. 2022;24(9):1840-1849. https://doi.org/10.1111/dom.14770
24. Fiorina P, Pozzilli P. Unveiling a novel type 1 diabetes endotype: opportunities for intervention. *Diabetes Metab Res Rev*. 2022;38(5):e3536. https://doi.org/10.1002/dmrr.3536
25. Waibel M, Thomas HE, Wentworth JM, et al. Investigating the efficacy of baricitinib in new onset type 1 diabetes mellitus (BANDIT)-study protocol for a phase 2, randomized, placebo controlled trial. *Trials*. 2022;23(1):433. https://doi.org/10.1186/s13063-022-06356-z
26. US National Library of Medicine. ClinicalTrials.gov. 2021. https://clinicaltrials.gov/ct2/show/NCT04838145