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Slowly progressive insulin-dependent diabetes mellitus in type 1 diabetes endotype 2

We have read with great interest the Review by Maria J. Redondo and Noel G. Morgan (Redondo, M.J., Morgan, N.G. Heterogeneity and endotypes in type 1 diabetes mellitus. *Nat. Rev. Endocrinol.* **19**, 542–554 (2023))[1]. The authors propose a new concept to clarify the intrinsically unique pathological processes in the heterogenous atypical endotype of type 1 diabetes mellitus (T1DE2) and to explore specific approaches for prediction, prevention and treatment. T1DE2 is sometimes assumed to be a mix of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) because a proportion of people with insulin-independent diabetes mellitus have islet autoantibodies, a marker of T1DM, as well as obesity and insulin resistance, markers of T2DM[1]. However, systematic data on pathobiological findings in pancreas tissue from people with T1DE2 are rarely reported, but there are some systematic studies on the endotype of typical type 1 diabetes mellitus (T1DE1)[2,3].

To make the concept of T1DE2 clearer, we present the distinct pathobiological findings of an atypical form of T1DM, slowly progressive insulin-dependent diabetes mellitus (SPIDDM)[4–7], as cited in the article[1]. SPIDDM onset predominantly occurs during adolescence or adulthood, and β-cell function usually decreases gradually until reaching the insulin-dependent stage[4,5]. In our study, people with SPIDDM had no history of obesity (defined as BMI >30.0 kg m^{-2}) (refs. 6,7). Most people with SPIDDM had T1DM-susceptible HLA-DR and HLA-DQ haplotypes[4,6].

The most predominant features of SPIDDM examined by in situ hybridization and immuno-histochemical methods indicate persistent enterovirus infection in the islet cells as well as in exocrine acinar cells[7]. Persistent enterovirus infection over decades in typical T1DM is not reported[2,3]. In addition, innate immune responses including melanoma associated protein 5 (MDA5), innate immune receptor and IFNβ1 expression gradually decreased with the duration of SPIDDM[7]. The suppressed innate immunity in SPIDDM was histologically related to the cleavage of MDA5 and IFNβ1 in islet cells by protease 2 ($2A^{pro}$) (ref. 7). $2A^{pro}$ is encoded by enteroviruses to cleave the enterovirus-preprotein to enable the assembly of the virus envelope protein[8]. $2A^{pro}$ potentially has proteolytic activity and could therefore damage neighbouring β-cells[7]. $2A^{pro}$ activity in coxsackie virus B3-induced chronic cardiomyopathy was reported to have a causative role on the cleavage and/or damage of cardiomyocyte dystrophin-glycoprotein complex[9].

The inflammation of islets in SPIDDM is less aggressive than in typical T1DM, probably due to a weakened innate immune response. This weakened innate immunity can be seen in the low numbers of infiltrating $CD8^+$ T cells in the pancreatic islets and the weak chemokine expression and MHC class I hyperexpression on β-cells in SPIDDM[6,7], sharply contrasting with the aggressive attack of $CD8^+$ T cells and cytopathic effects on β-cells observed in fulminant T1DM[10]. We could not find islet amylin polypeptide (IAPP)-positive amyloid deposition in the residual islet β-cells in SPIDDM[6], a marker of T2DM.

In summary, SPIDDM is strongly associated with persistent enterovirus infection that disables innate immunity through the MDA5–IFNβ1 axis and is associated with autoimmunity and T1DM-asssociated HLA haplotypes[4,6]. Association was not found with T2DM in our study; people with SPIDDM had no islet IAPP-amyloid deposition[6]. Our findings will contribute to the clarification of the T1DE2 endotype proposed by Redondo and Morgan[1].

There is a reply to this letter by Redondo, M. and Morgan, N. G. *Nat. Rev. Endocrinol.* https://doi.org/10.1038/s41574-024-00977-x (2024).

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Competing interests

The authors declare no competing interests.