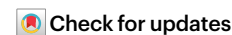


# Slowly progressive insulin-dependent diabetes mellitus in type 1 diabetes endotype 2



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))<sup>1</sup>. 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<sup>1</sup>. 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)<sup>2,3</sup>.

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)<sup>4–7</sup>, as cited in the article<sup>1</sup>. SPIDDM onset predominantly occurs during adolescence or adulthood, and  $\beta$ -cell function usually decreases gradually until reaching the insulin-dependent stage<sup>4,5</sup>. In our study, people with SPIDDM had no history of obesity (defined as BMI >30.0 kg m<sup>-2</sup>) (refs. 6,7). Most people with SPIDDM had T1DM-susceptible HLA-DR and HLA-DQ haplotypes<sup>4,6</sup>.

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<sup>7</sup>. Persistent enterovirus infection over decades in typical T1DM is not reported<sup>2,3</sup>. In addition, innate immune responses including melanoma associated protein 5 (MDA5), innate immune receptor and IFN $\beta$ 1 expression gradually decreased

with the duration of SPIDDM<sup>7</sup>. The suppressed innate immunity in SPIDDM was histologically related to the cleavage of MDA5 and IFN $\beta$ 1 in islet cells by protease 2 (2A<sup>pro</sup>) (ref. 7). 2A<sup>pro</sup> is encoded by enteroviruses to cleave the enterovirus-preprotein to enable the assembly of the virus envelope protein<sup>8</sup>. 2A<sup>pro</sup> potentially has proteolytic activity and could therefore damage neighbouring  $\beta$ -cells<sup>7</sup>. 2A<sup>pro</sup> activity in coxsackievirus B3-induced chronic cardiomyopathy was reported to have a causative role on the cleavage and/or damage of cardiomyocyte dystrophin-glycoprotein complex<sup>9</sup>.

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<sup>+</sup> T cells in the pancreatic islets and the weak chemokine expression and MHC class I hyperexpression on  $\beta$ -cells in SPIDDM<sup>6,7</sup>, sharply contrasting with the aggressive attack of CD8<sup>+</sup> T cells and cytopathic effects on  $\beta$ -cells observed in fulminant T1DM<sup>10</sup>. We could not find islet amylin polypeptide (IAPP)-positive amyloid deposition in the residual islet  $\beta$ -cells in SPIDDM<sup>6</sup>, a marker of T2DM.

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

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).

Tetsuro Kobayashi<sup>1,2</sup>✉ & Takashi Kadowaki<sup>1,3</sup>

<sup>1</sup>Department of Endocrinology and Metabolism, Toranomon Hospital, Tokyo, Japan.

<sup>2</sup>Division of Immunology and Molecular Medicine, Okinaka Memorial Institute for Medical Research, Tokyo, Japan. <sup>3</sup>Division of Endocrinology and Metabolism, Okinaka Memorial Institute for Medical Research, Tokyo, Japan.

✉ e-mail: [tetsurou@yamanashi.ac.jp](mailto:tetsurou@yamanashi.ac.jp)

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## Competing interests

The authors declare no competing interests.