Comment on: Greenbaum et al. Through the Fog: Recent Clinical Trials to Preserve β-Cell Function in Type 1 Diabetes. Diabetes 2012;61:1323–1330

Bernard Vialettes and René Valéro

The interesting article by Greenbaum et al. (1) attempts to trace future pathways toward curative treatments of type 1 diabetes by analyzing the lessons from the previously published trials, particularly those performed in recently diagnosed diabetic patients. The authors emphasize the constant finding observed in the trials with some efficacy on preservation of β-cell function (anti-CD3, anti–B cells, and CTLA-4 Ig), i.e., a biphasic evolution of C-peptide secretion. There was an early significant improvement of C-peptide secretion noted at 6 months in comparison with that in control subjects, but thereafter the C-peptide secretion decline paralleled that observed in the placebo groups. The authors interpreted this biphasic evolution by the coexistence of two pathogenic mechanisms involved in the β-cell loss. In addition to the chronic T-cell–mediated aggression of β-cells, which is targeted by the immune modulation, there is likely an acute inflammation not influenced by the treatment, which could have deleterious effects on the insulin secreting cells. We think that a third mechanism that has been proposed in a recently published commentary (2) should also be considered. We learned from rare nonautoimmune diabetes characterized by a specific loss of β-cells such as Wolfram disease, Wolcott-Rallison syndrome, or mutations in the insulin gene that the insulin-producing cells are exquisitely sensitive to endoplasmic reticulum (ER) stress (3). This system controls the synthesis of proteins by activating a defense machinery called unfolded protein response (UPR), which is supposed to correct defects in protein folding. If UPR is massively and/or chronically activated, the β-cells should turn toward apoptosis. The state of major reduction of β-cell mass such as that observed at the clinical onset of type 1 diabetes is particularly prone to a high secretion rate of insulin in the remaining cells, leading to misfolding and accumulation of proinsulin in ER. This ER stress induces an extensive activation of UPR and may consequently accelerate β-cell loss. Such mechanism could explain per se the persisting decline of C-peptide secretion despite a relative suppression of autoimmune processes by those active immunomodulators. It is also possible that the minor preservation of C-peptide secretion observed in the past with β-cell rest protocols using intensive insulin therapy (4) in recently diagnosed diabetic patients could be due to a decrease of ER load and an attenuation of UPR. We strongly suggest that this mechanism implicating ER stress in β-cell loss should also be taken into account in the future strategies to treat or prevent type 1 diabetes.

ACKNOWLEDGMENTS

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Greenbaum CJ, Schatz DA, Haller MJ, Sanda S. Through the fog: recent clinical trials to preserve β-cell function in type 1 diabetes. Diabetes 2012; 61:1323–1330
2. O'Sullivan-Murphy B, Urano F. ER stress as a trigger for β-cell dysfunction and autoimmunity in type 1 diabetes. Diabetes 2012;61:780–781
3. Fonseca SG, Gromada J, Urano F. Endoplasmic reticulum stress and pancreatic β-cell death. Trends Endocrinol Metab 2011;22:266–274
4. Shah SC, Malone JI, Simpson NE. A randomized trial of intensive insulin therapy in newly diagnosed insulin-dependent diabetes mellitus. N Engl J Med 1989;320:550–554

From the Department of Nutrition, Metabolic Diseases, and Endocrinology, Hospital "La Timone," Aix-Marseille University, Marseille, France.
Corresponding author: Bernard Vialettes, bernard.vialettes@ap-hm.fr.
DOI: 10.2337/db12-0834