What can we learn from the islet of Joslin Medalists?

The turn of 2019–2020 was a memorable time, as it was the 150-year anniversary of the discovery of pancreatic islets by Paul Langerhans (1869), and the 100-year anniversary of the discovery of insulin by Banting and Best (1921). With these glorious contributions, people with type 1 diabetes are now able to have a healthy life and are expected to survive to a full life expectancy. The Joslin Diabetes Center established 50-year gold medal awards for patients with type 1 diabetes who have lived >50 years, and named them “Medalists”. On this special occasion, there emerged accumulating data on the function and structure of the islet from 1,019 Medalists. The findings from the Medalists provide indispensable information to us on how to understand the natural history of type 1 diabetes and the underlying islet pathology (Figure 1).

We should first be reminded that children with features of type 1 diabetes do not all have an autoimmune basis, and that some have genetic causes. In the study, the age of the recruited patients was 6–15 years (median 11 years), and the majority of non-monogenic patients (938/1,018 patients, 92.1%) had autoimmune type 1 diabetes. However, 280 patients (27.5%) with monogenic diabetes variants were identified, which were likely pathogenic in 80 patients (7.9%). The recruited patients were subdivided into four groups based on the risk of human leukocyte antigen (HLA)-DR3 or HLA-DR4, and the presence of autoantibodies (Ab) to glutamic acid decarboxylase (GAD) and/or insulinoma associated antigen-1 (IA-1); Ab+/HLA+, Ab+/HLA−, Ab−/HLA+ and Ab−/HLA−. Among those, the Ab+/HLA− group was composed mainly of monogenic variants of hepatocyte nuclear factor-1 or other genes, whereas the autoimmune type was prevalent in the Ab+/HLA+ group, as expected. Some patients showed both the autoimmune and monogenic variant. The insulin secretory capacity by the mixed meal tolerance test in 516 Medalists, together with the evaluation of islet pathology on post-mortem pancreases of 68 Medalists were closely examined. There were no significant differences in the secretory capacity of C-peptide in response to meal stimuli or the population of residual β-cells among the subdivided groups. Thus, their findings appear to represent typical features of islet function and structure in Medalists who survived long time, and potentially provide useful information for the management of type 1 diabetes to maintain a good quality of life.

With the introduction of gene analysis, varieties of genetic diabetes are progressively increasing. In Medalists, the most popular among them were mutants of maturity onset diabetes of the young (MODY)-1 to MODY-5 genes encoding molecules related to insulin action and glycolytic pathways. Compared with patients with non-monogenic diabetes, monogenic diabetes variants showed higher levels of C-peptide and a higher prevalence of neuropathy. The number of patients with genetic diabetes studied was still too low to represent a specific phenotype of islet pathology. Nevertheless, β-cell loss was well characterized in cases of monogenic variants. Thus, for clinical management of type 1 diabetes, it is crucial to trace the family history for the identification of inheritance. Genetic analysis should be encouraged when the patient shows a high probability of inheritance.

Autoimmune attack of β-cells is a seminal feature in islets of the pancreas in type 1 diabetes patients. In the study of Medalists, Yu et al. attempted to characterize the islet pathology and distribution of residual β-cells (Figure 1). All the pancreases contained scattered singlet or doublet insulin-producing cells in a lobular pattern with a robust α-cell population. The β-cells were located as isolated or separated from original islets or often adjacent to ductal cells. However, cells that were newly derived from duct cells or other exocrine components were not clearly identified. It is known that there are some residual β-cells in type 1 diabetes long after the onset of diabetes. Meier et al. suggested that although remaining islet cells still have the capacity to regenerate (replication activity as measured by Ki67), β-cell death exceeds the rate of regeneration, resulting in progressive β-cell decline in long-standing type 1 diabetes. Consistent with previous studies, residual β-cells in Medalists underwent apoptotic cell death positive for terminal deoxynucleotidyl dUTP nick end labeling staining, while replicative cells were infrequent. It is thus likely that the destructive process of autoimmune attack sustains for a lifetime, but the concurrent presence of newly derived β-cells encourages the effort to explore regenerative therapy of islets for type 1 diabetes patients. The origin of residual endocrine cells has been the target of controversies. Meier et al. regarded residual β-cells as newly formed β-cells or transdifferentiated from α-cells in pre-existing islets.

*Corresponding author: Soroku Yagihashi
Tel: +81-43-243-9430
Fax: +81-43-243-9432
E-mail address: soroku.yagihashi@med.toho-u.ac.jp
Received 17 April 2020; revised 23 April 2020; accepted 24 April 2020
However, other sources of β-cells, such as ductal progenitor cells or uncommitted progenitor cells, or from transdifferentiation of other endocrine cells, might also be considered. In contrast, the findings of residual β-cells in singlets in Medalists’ pancreases suggests a survival or regeneration of β-cells under a long hyperglycemic milieu, and supports a waxing and waning process of β-cell remodeling in the presence of autoimmunity. Cross-sections at the end of life did not show the whole history of β-cells, and cannot lead to the final answer to the question on the exact origin of residual β-cells. Nevertheless, their presence long after the onset of diabetes indicates a dynamic process of islet remodeling, and might be the potential target to successful regenerative therapy for type 1 diabetes (Figure 1).

Information has been scarce on the capacity of insulin or glucagon secretion in long-standing type 1 diabetes. Surprisingly, insulin secretory capacity, as measured by C-peptide, although minimal, was maintained in one-third of the Medalists, among which 5.6% (30/516) responded well to the mixed meal tolerance test. The amount of residual β-cells correlated well with the insulin secretory capacity. It is interesting to note that antibody-negative individuals are more likely to show detectable levels of C-peptide, consistent with the preservation of β-cells, as are cases of monogenic diabetes variants. Ab-positive cases showed the least response to a meal, only at the minimally detectable levels of C-peptide. Thus, once the residual β-cells have been thought to be dormant, they are found to still be functionally active to respond to stimuli.

Diabetes is not limited to a disease of the endocrine pancreas, but involves the exocrine pancreas. There was not much discussion on the changes of the exocrine pancreas in the study of Medalists. Pancreas volume is reduced in patients with type 1 diabetes. The reason for this reduction has been ascribed to decreased

---

**Figure 1** | Implication of residual β-cells in Medalists. Young patients with type 1 diabetes are encountered in diverse conditions. The majority of those are autoimmune-mediated, but some patients with genetic origin might be included. A recent study disclosed the islet pathology and insulin secretory capacity in response to a meal test in long-lived patients with type 1 diabetes. Most cases showed the presence of residual β-cells in a lobular pattern. They were located as isolated in singlets in the exocrine area or near the duct, occasionally undergoing apoptosis with small infiltration of lymphocytes and macrophages. Such features indicate an ongoing islet remodeling influenced by autoimmune attack, as well as glucose toxicity, in Medalists. The origin of those cells was considered newly derived from pre-existing β-cells, transdifferentiated from α-cells or dedifferentiated from precursor cells, or budding from the ductal wall. Yet, a mixed meal tolerance test disclosed the insulin secretion capacity. They appeared to still contribute to the longevity and better quality of life of patients with type 1 diabetes. Changes of the exocrine pancreas remain to be explored in future investigations. T-ly, T-lymphocyte; Mφ, macrophage.
trophic action of insulin, showing atrophic exocrine pancreas. Sustained inflammation is also suggested to contribute to pancreatic atrophy, because patients with type 1 diabetes often manifest widespread infiltration of lymphocytes and plasma cells, as well as macrophages in the exocrine pancreas and around duct tissues. Duct-centric inflammatory changes might also confer the lobular distribution of islet pathology, as detected in Medalists. Concurrent with inflammatory changes, lesions of intraductal proliferation of ductal cells are frequently encountered in patients with long-term diabetes. We should be aware that the prevalence of pancreatic cancer is nearly double in people with diabetes compared with people without diabetes. Mutual relationships during oncogenesis between the endocrine and exocrine pancreas are largely unknown and, therefore, this field awaits further exploration.

As evident from valuable studies of Medalists, type 1 diabetes includes considerable population of monogenic variants, which should be remembered in clinical practice. Currently, there are quite a few options for insulin treatment, so the longevity of patients with type 1 diabetes is surprisingly improved. For further improvement of quality of life for patients with type 1 diabetes, data from Medalists provided a seed for the exploration of effective regenerative therapy of functioning β-cells. With longer survival of patients, we might then be ahead with new battles against the occurrence of neoplasms.

DISCLOSURE
The author declares no conflict of interest.

Soroku Yagihashi1,2,*
1Department of Exploratory Medicine for Nature, Life and Human, Toho University School of Medicine, Chiba, Japan, 2Department of Pathology and Molecular Medicine, Hirosaki University Graduate School of Medicine, Hirosaki, Japan

REFERENCES
1. Keenan HA, Sun JK, Levine J, et al. Residual insulin production and pancreatic β-cell turnover after 50 years of diabetes: Joslin Medalist study. Diabetes 2010; 59: 2846–2853.
2. Yu MG, Keenan HA, Shah HS, et al. Residual β cell function and monogenic variants in long-duration type 1 diabetes patients. J Clin Invest 2019; 129: 3252–3263.
3. Lühr M, Klöppel G. Residual insulin positivity and pancreatic atrophy in relation to duration of chronic Type 1 (insulin-dependent) diabetes mellitus and microangiopathy. Diabetologia 1987; 30: 757–762.
4. Meier JJ, Bhushan A, Butler AE, et al. Sustained beta cell apoptosis in patients with long-standing type 1 diabetes: indirect evidence for islet regeneration? Diabetologia 2005; 48: 2221–2228.
5. Schlu di B, Moin ASM, Montemurro C, et al. Islet inflammation and ductal proliferation may be linked to increased pancreatitis risk in type 2 diabetes. JCI Insight 2017; 2: pii: 92282.

Doi: 10.1111/jdi.13283