Diabetol Int (2016) 7:101–103
DOI 10.1007/s13340-016-0266-y

EDITORIAL

More β-cell researchers are wanted!

Susumu Seino[1]

Received: 14 March 2016 / Published online: 8 April 2016

β-cell research has been advancing rapidly since the beginning of the twenty-first century. By the 1960s it was known that β-cell dysfunction is a primary mechanism underlying the pathophysiology of type 2 diabetes mellitus (T2DM), as a low insulin secretory response to glucose infusion was found in patients with T2DM [1]. In the 1980s, the β-cell dysfunction hypothesis was further supported by the finding that insulin secretion is severely but selectively impaired in response to glucose stimulation in T2DM [2]. However, from the 1980s to the 1990s, T2DM was regarded as primarily a disease arising from insulin resistance. Research on insulin action dominated diabetology, with many leading research groups neglecting β-cells and focusing almost exclusively on the mechanisms of insulin signaling and the relationship between insulin resistance and diabetes. This state of affairs changed drastically, however, in the late 1990s, when it was found that all of the MODY (maturity onset diabetes of the young) genes and many of the T2DM susceptibility genes identified by GWAS are associated with β-cell function and/or development. It is now widely accepted that T2DM does not develop without insufficient β-cell function and/or mass, and this recognition has drawn the attention of many diabetologists to β-cell research. Nearly all research groups now recognize the importance of β-cell function and/or mass in the pathogenesis and pathophysiology of T2DM, and are presently engaged in β-cell research. The number of publications on β-cell research has rapidly increased according to our PubMed search for publications using the keywords "pancreatic β-cell," "β-cell differentiation," and "β-cell regeneration" (Fig. 1). Major current themes of β-cell research include (1) mechanisms for the regulation of insulin secretion, (2) mechanisms of β-cell fate, and (3) mechanisms of β-cell failure in T2DM. With regard to the first of these research themes, although elucidation of the signaling mechanisms in insulin secretion has long been pursued, recent advances in the technologies of proteomics and metabolomics have made it possible for us to identify many novel downstream signals and targets of well-known second messengers such as Ca^{2+}, cAMP, diacylglycerol (DAG), and inositol 1,4,5-triphosphate (IP_3), which has revealed that various known metabolites in glucose metabolism and lipid metabolism are important cell signals in insulin secretion. Furthermore, a variety of proteins, mostly those called cytokines—which are secreted from adipose tissues (adipokines), liver (hepatokines), and muscles (myokines)—are now known to affect β-cell function and mass; these molecules mediate the interaction between β-cells and insulin-target tissues. Although our understanding of the roles of intra- and extra-β-cell signals in insulin secretion has increased greatly in recent years, the mechanism by which these signals are integrated to precisely regulate insulin secretion in vivo remains to be clarified. Elucidation of the mechanisms of the interactions among α-, β-, and δ-cells and their physiological and pathophysiological roles, although a well-trodden research path, is yet to be achieved. Regarding theme (2), in the past decade we have accumulated considerable knowledge of the differentiation of stem (progenitor) cells into β-cells and their development, death, and regeneration [3]. Dedifferentiation of β-cells and transdifferentiation between β-cells and non-β-cells are also attractive topics. Until recently, investigators attempted to study β-cell fate through morphological analyses, which severely limited

✉ Susumu Seino
seino@med.kobe-u.ac.jp

[1] Division of Molecular and Metabolic Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

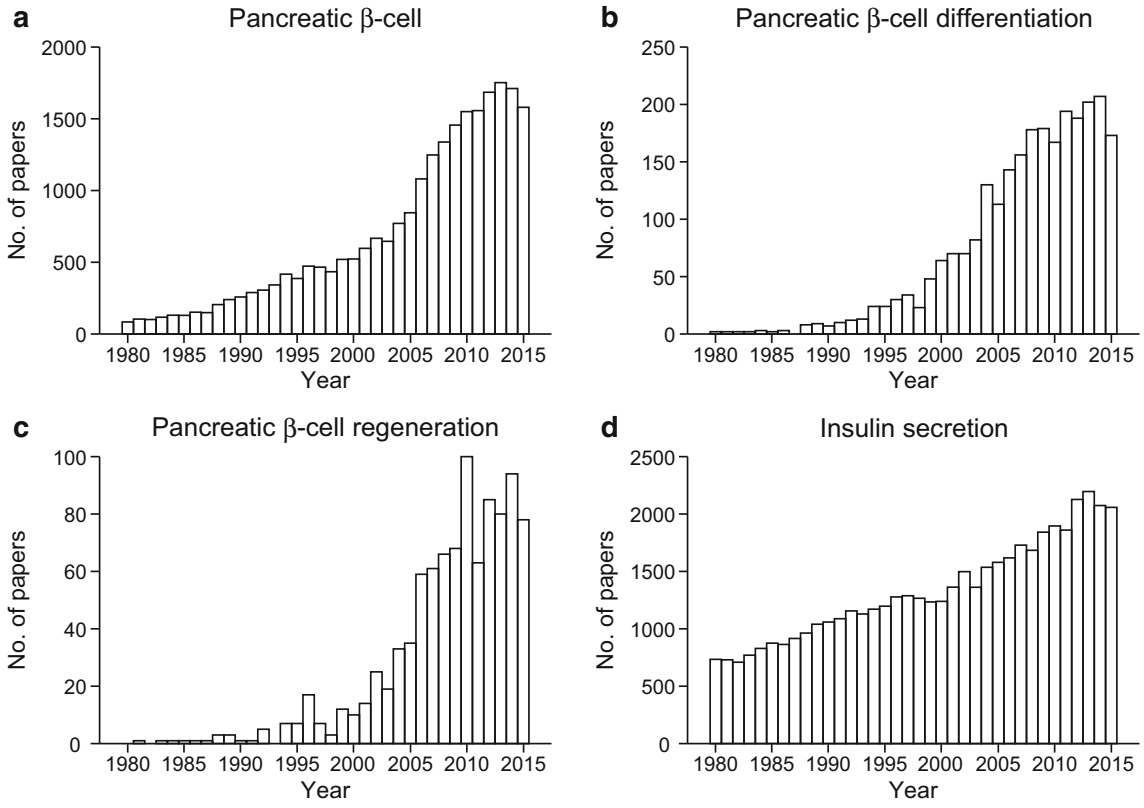

Fig. 1 Changes in the number of publications related to β-cell research over time

their ability to confirm and test hypotheses. Although powerful tools to track cell lineage have now been developed that enable great advances, the signaling mechanisms governing β-cell fate remain unclear, and it is a mystery how the insulin secretory apparatus, including glucose sensing, metabolism–secretion coupling, and exocytosis, is acquired in the process of differentiation into mature β-cells. We also need to accumulate data on β-cell fate in normal human subjects to learn how it is altered in diabetes; this should facilitate the development of novel therapies and allow us to clarify the pathophysiology of diabetic β-cells (notwithstanding the methodological difficulties involved). Considering research theme (3), the study of β-cell failure has focused mainly on the mechanisms of endoplasmic reticulum (ER) stress and oxidative stress (which eventually induce β-cell apoptosis), and their relationships with glucotoxicity and lipotoxicity [4]; there are additional promising areas of research on this theme, each of which is ripe for development. Autophagy is a topic currently attracting interest in terms of the relationship between turnover of cellular organelles and β-cell function. Amyloid deposition in the pancreatic islets has long been known to be a characteristic feature of T2DM. Islet amyloid polypeptide (IAPP or amylin) is the major component of islet amyloid. Amyloid formation is considered to lead to β-cell dysfunction and cell death. However, the mechanisms of islet amyloid-induced cytotoxicity in T2DM remain largely unexplained [5]. Another potentially productive research area in β-cell failure is the various interactions of β-cell function with environmental factors (e.g., endocrine disruptors such as arsenic), as well as genetic and epigenetic factors. This is especially relevant to the task of solving the evolving diabetes epidemic in developing countries [6]. Due to the development of new techniques and our understanding of β-cell biology, the research areas included in these three themes represent numerous and increasing opportunities for investigators, both established and new, to develop novel diabetes therapies.

From a therapeutic point of view, there are two trends in strategies targeting β-cells: regeneration of β-cells and improvement of β-cell function (i.e., insulin secretion). The former includes the development of various peptides and small-molecule compounds to induce the proliferation of existing β-cells in vivo as well as the establishment of efficient methods for the differentiation of embryonic stem cells or induced pluripotent stem cells into β-cells in vitro [7]. However, there are many challenges that must be surmounted before these techniques can be translated to clinical practice. On the other hand, the strategy for

improving β-cell function includes developing insulin secretagogues with novel mechanisms (targets), especially those that improve glucose metabolism in β-cells. Small-molecule compounds that suppress ER stress and oxidative stress, if discovered, would also be promising new antidiabetic drugs to protect β-cell function and mass.

It is therefore clear that without leading-edge β-cell research, we will not be able to elucidate the mechanisms of diabetes progression or dramatically improve its treatment. A seminal article entitled "Insulin biosynthesis and secretion—a still unsettled topic," published in the NEJM by Albert Renold 45 years ago [8], might have awakened us to the central problem that represents our urgent challenge today. Although β-cell research includes many diverse areas, the number of β-cell researchers is currently insufficient to solve these many important and interesting issues. Is this due to the fact that β-cell research is especially difficult both methodologically and practically? Whatever the reason, we should ask ourselves if we are investing sufficient effort into nurturing β-cell researchers. To cure diabetes, it is vitally important to encourage and nurture today's young scientists who will be responsible for β-cell research in the future. More β-cell researchers, whether they are physician-scientists or basic scientists, are needed.

Compliance with ethical standards

Ethics policy Not applicable.

References

1. Cerasi E, Luft R. The plasma insulin response to glucose infusion in healthy subjects and in diabetes mellitus. Acta Endocrinol. 1967;55:278–304.
2. Ward MK, Bolgiano DC, McKnight B, Halter JB, Porte D Jr. Diminished β-cell secretory capacity in patients with noninsulin-dependent diabetes mellitus. J Clin Invest. 1984;74:1318–28.
3. Minami K, Seino S. Current status of regeneration of pancreatic β-cells. J Diabetes Investig. 2013;4:131–41.
4. Accili D, Ahren B, Boitard C, Cerasi E, Henquin JC, Seino S. Special issue: The stressed beta-cell. Proceedings of the 11th Servier-IGIS symposium, St. Jean Cap Ferrat, France, 25–28 March 2010. Diabetes Obes Metab. 2010;12(S2):1–167.
5. Cao P, Marek P, Noor H, Patsalo V, Wang H, Abedini A, Releigh DP. Islet amyloid: from fundamental biophysics to mechanisms of cytotoxicity. FEBS Lett. 2013;587:1106–18.
6. Sargis RM. The hijacking of cellular signaling and the diabetes epidemic: mechanisms of environmental disruption of insulin action and glucose homeostasis. Diabetes Metab J. 2014;38:13–24.
7. Schiesser JV, Wells JM. Generation of β cells from human pluripotent stem cells: are we there yet? Ann NY Acad Sci. 2014;1311:124–37.
8. Renold AE. Insulin biosynthesis and secretion—a still unsettled topic. N Engl J Med. 1970;282:173–82.