Editorial Overview

Editorial Overview: "Islet Biology in Type 2 Diabetes"

The prevalence of obesity, prediabetes, and full-blown type 2 diabetes (T2D) is steadily increasing all over the world, including in adolescents and young adults. In the majority of patients, T2D results from the inability of the endocrine pancreas to fully compensate for insulin resistance in a context of predisposing environmental and genetic factors. At first sight, it could seem easier to prevent T2D by reducing insulin resistance, i.e., by promoting a healthy diet and increased physical activity. However, despite its success in highly motivated patients, this strategy has so far globally failed to reduce the incidence of T2D at the population level. Another approach is to try to better understand why the endocrine pancreas fails to secrete enough insulin or why it secretes too much glucagon in T2D patients, so that we can then try to prevent the progression from prediabetes to T2D or even revert from T2D to normal glucose tolerance. This special issue highlights some of the progress made over the last decade in this area of intense research.

Understanding the pathophysiology of the endocrine pancreas in T2D is not possible without a full understanding of its development during embryogenesis, regulation of its mass and cell identity throughout life, and the control of hormonal secretion under physiological conditions. It also requires an understanding of how these processes are affected by exposure to environmental factors associated with insulin resistance, i.e., sustained changes in nutrient supply, and how genetic factors that predispose individuals to T2D interact with these processes under normal and insulin resistant states.

The first section of this special issue on "islet biology in type 2 diabetes" deals with new aspects of hormone secretion and exocytosis by the different islet cell types and their interaction within the islets of Langerhans that constitute the endocrine pancreas. The paper by Thurmond and Gaisano [1] details the recent understanding of and some controversies regarding the insulin granule exocytotic machinery in health and T2D. Calcium, being the most important fusogenic signal for insulin granule exocytosis, its complex handling in the β-cell involving a variety of plasma membrane ion channels, and how they are perturbed are critically discussed in the paper by Jacobson and Shyng [2]. Currently, glucagon-like peptide-1-based therapies are the most exciting treatment strategy for T2DM; and here some new insights into the precise GLP-1 receptor signaling for preservation of β-cell function and mass are critically reviewed by Tomas, Jones, and Leech [3]. The islet defect in T2D is not entirely attributed to just the β-cell secretory deficiency, but very much contributed by perturbation in alpha-cell glucagon secretion and additional novel cues within the islet microenvironment that were only very recently revealed. Alpha-cell dysfunction accounts for most of the commonly observed hyperglucagonemia, which contributes to hyperglycemia and alpha-cell glucose blindness into exogenous insulin-induced hypoglycemia by still incompletely understood mechanisms here reviewed by Gilon [4]. Whereas it has been well accepted that paracrine interactions between islet cells are dysregulated in T2D, there is now a better understanding of β-cell heterogeneity and their complex coupling within a network whereby leader or "hub" cells could directly control the β-cell network and failure of the leader cells could conceivably shutdown the network; this intriguing new insight has been proposed by Da Silva Xavier and Rutter [5]. A more comprehensive understanding of the islet microenvironment is reviewed by Lammert and Thorn [6] whereby they proposed to extend to the immediate surrounding contact of islet endocrine cells with the vasculature that contributes to the concept of the islet "niche," which can confer functional specialization mimicking a polarized secretory cell. MicroRNAs are small noncoding RNAs found to be important regulators of gene expression, which can be profoundly affected by T2D insults (hyperglycemia, hyperlipidemia) and contribute to the β-cell secretory defects; this topic reviewed by Eliasson and Regazzi [7].

The second section of this special issue focuses on recent aspects of nutrient metabolism in pancreatic β-cells. Acceleration of nutrient metabolism is key to the regulation of insulin secretion but also to many other events that are involved in the long-term adaptation of β-cell mass and function to changes in insulin demand and in the development of T2D. The paper by Spégel and Mulder [8] critically reviews how metabolomics studies have changed our understanding of the metabolic changes triggered by nutrient stimulation in islets

and β-cells under control and T2D conditions. The long-recognized increase in NADH and concomitant decrease in NAD^+ in nutrient stimulated β-cells were recently shown to exert large effects on protein acetylation through changes in sirtuin activity, and the paper by Santo-Domingo, Dayon, and Wiederkehr [9] presents how protein lysine acetylation contributes to the regulation of mitochondrial metabolism in β-cell under physiological conditions and how protein lysine hyperacetylation under conditions related to T2D (nutrient toxicity, oxidative stress) impairs mitochondrial function. Whether nutrient stimulation triggers β-cell oxidative stress is a highly debated topic in the field, and the paper by Roma and Jonas [10] critically reviews recent data about the acute and chronic effects of nutrients on islet cell redox state with a focus on their subcellular compartmentation. The role of lysosomes in nutrient sensing is an emerging field in β-cell metabolism. The paper by Vivot, Pasquier, Goginashvili, and Ricci [11] presents recent data about how nutrient-dependent lysosomal function influences insulin secretion and β-cell health and discusses its role in the context of β-cell failure in diabetes. A comprehensive overview of past and recent advances about the mechanisms by which nutrient oversupply is toxic to β-cell function and survival in the context of T2D is then presented by Lytrivi, Castell, Poitout, and Cnop [12].

The third section focuses on how human genetics has shaped our understanding of pancreatic islet cell function through genetic discoveries for both monogenic forms of diabetes and T2D. This is an area where the field has witnessed substantial progress over the last 10 years through the collision of technological advancements, which has allowed genome-wide interrogation of genetic variation and large international collaborative initiatives. De Franco [13] covers the genetic basis for neonatal diabetes where human genetics has not only provided critical insights into human pancreatic islet development but also led to changes in the framework for patient treatment and management. Mattis and Gloyn [14] provide a comprehensive overview of our current understanding of the genetic landscape for T2D focusing on the evidence of a critical role for pancreatic islet-cell dysfunction. They illustrate the different approaches that need to be adopted to move from a genetic association signal to a molecular mechanism for islet-cell dysfunction and how new and emerging human β-cell models are playing a vital role in these endeavors. Finally, Kettunen and Tuomi [15] share their insights on using humans as a model system through physiological characterization of genetic defects in islet-cell function. They discuss the commonly used tests with examples drawn from both monogenic and type 2 diabetes highlighting the challenges and limitations of these tests, not least the inability to distinguish between defects in β-cell mass and function.

The breadth and depth of the collection of fifteen articles presented in this Special Issue provide considerable insight into the complexity of the various aspects of islet biology that collectively contribute to the pathogenesis of T2D. Each article is a timely review and a balanced critique of its respective large body of work, offering insights into lingering controversies and providing future directions to pursue in order to address many unanswered questions. This issue therefore provides for both the novice and experts a firm foundation for understanding islet biology in T2D.

References

[1] D. Thurmond, H. Gaisano, Recent insights into beta-cell exocytosis in type 2 diabetes, J. Mol. Biol. (2020), https://doi.org/10.1016/j.jmb.2019.12.012.

[2] D. Jacobson, S.-L. Shyng, Ion channels of the islets in type 2 diabetes, J. Mol. Biol. (2020) 1–21, https://doi.org/10.1016/j.jmb.2019.08.014.

[3] A. Tomas, B. Jones, C. Leech, New insights into beta-cell GLP-1 receptor and cAMP signaling, J. Mol. Biol. (2020), https://doi.org/10.1016/j.jmb.2019.08.009.

[4] P. Gilon, The role of α-cells in islet function and glucose homeostasis in health and type 2 diabetes, J. Mol. Biol. (2020).

[5] G. Da Silva Xavier, G.A. Rutter, Metabolic and functional heterogeneity in pancreatic β cells, J. Mol. Biol. (2020) 2–13, https://doi.org/10.1016/j.jmb.2019.08.005.

[6] E. Lammert, P. Thorn, The role of the islet niche on beta cell structure and function, J. Mol. Biol. (2020) 1–12, https://doi.org/10.1016/j.jmb.2019.10.032.

[7] L. Eliasson, R. Regazzi, Micro(RNA) management and mismanagement of the islet, J. Mol. Biol. (2020) 1–10, https://doi.org/10.1016/j.jmb.2019.09.017.

[8] P. Spégel, H. Mulder, Metabolomics analysis of nutrient metabolism in β-cells, J. Mol. Biol. (2020), https://doi.org/10.1016/j.jmb.2019.07.020.

[9] J. Santo-Domingo, L. Dayon, A. Wiederkehr, Protein lysine acetylation: grease or sand in the gears of β-cell mitochondria? J. Mol. Biol. (2020) https://doi.org/10.1016/j.jmb.2019.09.011.

[10] L.P. Roma, J.-C. Jonas, Nutrient metabolism, subcellular redox state and oxidative stress in pancreatic islets and β-cells, J. Mol. Biol. (2020), https://doi.org/10.1016/j.jmb.2019.10.012.

[11] K. Vivot, A. Pasquier, A. Goginashvili, R. Ricci, Breaking bad and breaking good: β-cell autophagy pathways in diabetes, J. Mol. Biol. (2020), https://doi.org/10.1016/j.jmb.2019.07.030.

[12] M. Lytrivi, A.-L. Castell, V. Poitout, M. Cnop, Recent insights into mechanisms of β-cell lipo- and glucolipotoxicity in type 2 diabetes, J. Mol. Biol. (2020), https://doi.org/10.1016/j.jmb.2019.09.016.

[13] E. De Franco, From biology to genes and back again: gene discovery for monogenic forms of beta-cell dysfunction in diabetes, J. Mol. Biol. (2020), https://doi.org/10.1016/j.jmb.2019.08.016.
[14] K. Mattis, A.L. Gloyn, From genetic association to molecular mechanisms for islet-cell dysfunction in type 2 diabetes, J. Mol. Biol. (2020) 1–13.
[15] J.L. Kettunen, T. Tuomi, Human physiology of genetic defects causing beta-cell dysfunction, J. Mol. Biol. (2020) 1–9.

Herbert Y. Gaisano
Departments of Medicine and Physiology, University of Toronto and The Toronto General Hospital Research Institute, Toronto, Ontario, Canada
Correspondence to Herbert Y. Gaisano.
E-mail address: herbert.gaisano@utoronto.ca

Jean-Christophe Jonas
Université catholique de Louvain (UCLouvain), Institute of Experimental and Clinical Research, Pole of Endocrinology, Diabetes and Nutrition, Brussels, Belgium

Anna L. Gloyn
Oxford Centre for Endocrinology and Metabolism, Radcliffe Department of Medicine and Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, UK NIHR Oxford Biomedical Research Centre, Churchill Hospital, Oxford, UK

Edited by Herbert Gaisano