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100 Years of Glucagon Anniversary, Special Collection – Editorial

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Abstract

The year 2023 marks 100 years since publication of the first report of a hyperglycemic factor in pancreatic extracts which CP Kimball and John R Murlin named glucagon (from GLUCose AGONist). Glucagon has a range of profound effects on metabolism including, but not limited to, stimulation of hepatic glucose production. Dysregulation of glucagon secretion is a key feature of both major forms of diabetes, leading to the concept that diabetes is a bihormonal disorder. Still, work to fully understand the production and biological effects of glucagon has proceeded at a slower pace compared to that of insulin. A recent resurgence of interest in the islet α cell, the predominant site of glucagon production, has been facilitated in part by technological innovations. This work has led to significant developments in the field, from defining how alpha cells develop, how glucagon is secretion from pancreatic alpha cells is regulated, through to determining the role of glucagon in metabolic homeostasis and the progression of both major forms of diabetes. In addition, glucagon is considered to be a promising target for diabetes therapy, with many new potential applications arising from research in this field. This collection of reviews, led by Guest Editors James Cantley, Rebecca Hull-Meichle and Vincent Poitout, is intended to capture the field's current understanding of glucagon and alpha cell biology, as well stimulate additional interest and research on this important hormone.

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Glucagon, the principal hormone produced by pancreatic islet α cells, has a range of profound effects on metabolism including, but not limited to, stimulation of hepatic glucose production. Accordingly, glucagon has been utilised as a first line treatment for severe hypoglycemia since the 1950s (Elrick et al., 1958). Dysregulation of glucagon secretion is a key feature of both major forms of diabetes, leading to the concept that diabetes is a bihormonal disorder (Unger and Orci, 1975). The year 2023 marks 100 years since publication of the first report of a hyperglycemic factor in pancreatic extracts which CP Kimball and John R Murlin named glucagon (from GLUCose AGONist; (Kimball and Murlin, 1923)). This report was made around the same time, and indeed was part of the same process that led to the discovery of insulin (Banting et al., 1922, Cantley and Eizirik, 2021). Similarly, although much earlier, the first description of α cells (or "A cells") and β cells in the pancreatic islet was also made concurrently (Lane, 1907); these are now recognised as glucagon- and insulin-producing cells, respectively (Baum et al., 1962, Lacy and Davies, 1957, Lacy and Davies, 1959) (see Figure 1 from Gao et al for a timeline).

Despite the close temporal discovery of glucagon and insulin, work to fully understand the production and biological effects of glucagon has proceeded at a much slower pace than that of insulin. An early contributor to this was the controversy surrounding glucagon's identity as a hormone. Only following its purification (Staub et al., 1953, Staub et al., 1955), sequencing (Bromer et al., 1957) and development of the first glucagon radioimmunoassay by Roger Unger in 1959 (Unger et al., 1959, Unger et al., 1961) could work on glucagon proceed in earnest.

Despite 100 years of research, the knowledge gap between glucagon and insulin secretion and action still exists. Aspects of α cell development, differentiation and identity including inter-species differences, along with the physiological regulation of glucagon secretion during health, and how this becomes dysregulated in diabetes, all remain relatively poorly understood. Encouragingly, a recent resurgence of interest in the islet α cell and glucagon has led to an acceleration in research on this topic (as illustrated in Figure 1 from Pettway et al). Based, in part on this resurgence in research interest, glucagon is considered to be a promising target for diabetes therapy.

This special collection of 7 reviews captures the field's current understanding of glucagon and α cell biology, and is intended to stimulate additional interest and research on this important hormone. The introductory article in this collection, by Paul Robertson (Robertson), provides a historical perspective on the physiological role of glucagon and discusses the interplay between glucagon and insulin, especially in the context of response to hypoglycemia.

Brooks and Sussel (Brooks et al) provide an overview of α cell specification and development, and review evidence for the inherent proliferative capacity of α cells, a feature which (especially in adults) distinguishes them from β cells, which have a much more limited proliferative capacity. The article also details regulation of α cell identity, which remains incompletely understood but has recently been illuminated by technological advances (e.g. single cell transcriptomics). Finally, the authors describe the epigenetic plasticity of α cells, which may underlie the loss of α cell identity and impaired function observed in diabetes.

The next two articles (Gao et al and Armour et al) review the elegant combination of intracellular molecular mechanisms utilised by alpha cells to confer the unique glucagon secretory response to low blood glucose concentrations, counter-regulatory to β cells. Gao, Ma, Wendt and Zhang focus on the electrophysiology of the α cell and how this is coupled to glucagon secretion in response to nutrient, paracrine and neural stimulation. Armour, Stanley, Cantley, Dean and Knudsen provide a complementary review focusing on the metabolic mechanisms underlying

nutrient sensing in the α cell. They emphasise the important roles of non-glucose fuels, principally amino acids and lipids, in α cell metabolic activity and how this links glucagon secretion with systemic metabolism. These may be especially important given that α cell secretory activity is high when prevailing glucose levels are low. These reviews also touch on important, but still understudied, similarities and differences between human and rodent α cells.

Pettway, Saunders and Brissova (Pettway et al) delve more deeply into our current understanding of the human α cell, both in terms of morphology and function. This article highlights how the α cell is positioned to produce and receive paracrine/juxtacrine signals, the contribution of transcriptomics to better understand regulation of α cell identity and how the α cell responds to physiological (aging, pregnancy) and pathological (obesity, diabetes) challenges.

Kaur and Seaquist (Kaur et al) review the multiple physiological actions of glucagon, including its role in amino acid and lipid metabolism in liver and fat and in thermogenesis. This review also focuses on translational aspects of glucagon, along with current and potential future therapeutic applications. These include closed loop bihormonal pumps for diabetes treatment and review of work investigating glucagon receptor blockers as potential anti-diabetes therapies.

Rounding out this outstanding collection of reviews is the article by Panzer and Caicedo (Panzer et al) which provides an engaging narrative on the evolution of glucagon and α cell research. The authors provide a forward-looking perspective on the role of emerging technologies to catalyse scientific advancement, and call for imaginative and transformative approaches to launch the next 50-100 years of research on glucagon and the α cell.

Declaration of interest

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