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Up front

Competition for publication in *Diabetologia* continues to grow, and less than 20% of papers are accepted. Of all the high-quality papers that appear in this month's issue I want to draw your attention to five articles that I think are particularly interesting. The articles are summarised here. Our publisher, Springer, has kindly made the full text of each of these papers freely available.
I hope you enjoy reading them!

Sally M. Marshall, Editor

Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition

Volker Vallon, Scott C. Thomson

The EMPA-REG OUTCOME trial revealed that the addition of the sodium glucose cotransporter 2 (SGLT2) inhibitor empagliflozin to standard care for patients with type 2 diabetes and high cardiovascular risk delayed the progression of kidney disease and lowered rates of clinically relevant renal and cardiovascular events. This exciting and promising news for the diabetes field provided a new glucose lowering approach, for which the primary target is the kidney. In this issue, Vallon and Thomson summarise the role of SGLT2 in the physiology and pathophysiology of renal glucose reabsorption. The authors outline the metabolic benefits of enhancing urinary glucose excretion while leaving metabolic regulation and counterregulation intact. They also discuss the pleiotropic impact of SGLT2 inhibition, which creates a favourable environment for beneficial and synergistic effects on metabolism and the renal and cardiovascular systems. In doing so, they outline the unexpected logic of inhibiting SGLT2 in the kidney of individuals with diabetes.

Glia: silent partners in energy homeostasis and obesity pathogenesis

John D. Douglass, Mauricio D. Dorfman, Joshua P. Thaler

The discovery of new brain mechanisms for governing food intake and energy expenditure is critical for the development of novel drugs to target obesity. In this issue, Douglass et al review recent studies, revealing a previously unappreciated role for non-neuronal cells in the regulation of energy homeostasis and obesity susceptibility. Glia, the most numerous cells of the central nervous system, are involved in nearly all brain functions, from neurovascular coupling and blood–brain barrier maintenance to modulation of synaptic activity and protection against pathogens. In the context of energy homeostasis, glia promote hypothalamic inflammation, neuronal stress and overconsumption in response to high-fat diets. In addition, glial cells directly respond to circulating nutrients and critical adiposity hormones, such as leptin and insulin, providing an additional mechanism for body weight regulation. Thus, investigating glial contributions to energy balance holds great promise for identification of new targets for the treatment of obesity and metabolic disease.

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A longitudinal study of iron status during pregnancy and the risk of gestational diabetes: findings from a prospective, multiracial cohort

Shristi Rawal, Stefanie N. Hinkle, Wei Bao, Yeyi Zhu, Jagteshwar Grewal, Paul S. Albert, Natalie L. Weir, Michael Y. Tsai, Cuilin Zhang

Iron overload is implicated in impaired glucose metabolism among non-pregnant populations. Iron status changes dramatically throughout pregnancy, yet the trimester-specific association between iron levels in pregnancy and subsequent risk of gestational diabetes (GDM) is unknown. In this issue, Rawal et al report prospective findings from a longitudinal study that examined the associations between GDM risk and gestational iron status. Iron status was characterised by a comprehensive panel of traditional and novel iron biomarkers. Pregnant women with very high levels of iron biomarkers (i.e. ferritin and hepcidin) in either the first or second trimester of pregnancy had an increased risk of GDM, with stronger associations appearing in the second trimester. Although there are known benefits of iron supplementation for iron-deficiency in pregnancy, findings from the present study suggest that elevated iron stores in pregnant women may be involved in the development of GDM and, thus, raise potential concerns about routine iron supplementation among pregnant women with sufficient iron levels. This article is the subject of a commentary in this issue by Aidan McElduff.

Adipocyte STAT5 deficiency promotes adiposity and impairs lipid mobilisation in mice

Doris Kaltenecker, Kristina M. Mueller, Pia Benedikt, Ursula Feiler, Madeleine Themanns, Michaela Schlederer, Lukas Kenner, Martina Schweiger, Guenter Haemmerle, Richard Moriggl

Dysfunctional lipid metabolism in white adipose tissue contributes to various diseases. Thus, it is essential to delineate molecular mechanisms that regulate lipid handling in adipocytes. In this issue, Kaltenecker, Mueller et al report that the transcription factor signal transducer and activator of transcription 5 (STAT5) is an important modulator of white adipose tissue function in mice. Adipocyte-specific STAT5 deficiency markedly reduced basal lipolysis rates, resulting in a higher body fat content in STAT5-deficient mice vs controls. They demonstrate that STAT5 is directly involved in the gene regulation of the lipid-cleaving enzyme adipose triglyceride lipase (ATGL, encoded by *Pnpla2*), uncovering a new mechanism for the regulation of lipolysis in adipose tissue. Interestingly, despite the increased adiposity, STAT5-deficient mice were metabolically healthier and remained more insulin sensitive with ageing compared with controls. This study provides a basis for future investigation into the extent to which the inhibition of STAT5 in adipose tissue might constitute a therapeutic intervention strategy for metabolic diseases.

Insulitis in human diabetes: a histological evaluation of donor pancreases

Marcus Lundberg, Peter Seiron, Sofie Ingvast, Olle Korsgren, Oskar Skog

According to the consensus criteria developed for type 1 diabetes, an individual can be diagnosed with insulitis when $\geq$15 $CD45^+$ cells are found within the parenchyma or in the islet–exocrine interface in $\geq$3 islets. In this issue, Lundberg et al report that, overall, 28% (14 out of 50) of donors with type 2 diabetes and 31% of donors with type 1 diabetes (four of 14 donors) fulfilled these consensus criteria for insulitis. In contrast, only type 1 diabetic donors had $\geq$15 $CD3^+$ cells in $\geq$3 islets. From these findings, the authors conclude that the current definition of insulitis cannot be used to distinguish pancreases retrieved from individuals with type 1 diabetes from those with type 2 diabetes. As a consequence, they propose a revised definition of insulitis in type 1 diabetes, with a positive diagnosis when $\geq$15 $CD3^+$ cells (not $CD45^+$ cells) are found in $\geq$3 islets.

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