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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

Emerging role of intestinal microbiota and microbial metabolites in metabolic control

Hilde Herrema, Richard G. IJzerman, Max Nieuwdorp

Gut microbiota and microbial metabolites (including short-chain fatty acids) have been increasingly associated with the development of metabolic diseases, including obesity and type 2 diabetes. Nevertheless, experimental data showing causality in humans is limited and such data primarily originate from rodent studies. In this issue, Herrema et al comment on two recent rodent studies, one of which investigated the interaction between environmental and genetic factors in microbiota-related metabolic disease development in mice and the other studied the potential mechanism underlying microbiota-driven disease development in rats. Referring to these publications, Herrema et al discuss how specific interventions, including faecal transplantation, gastric bypass and antibiotic treatment, and environmental factors (e.g. experimental facility and dietary challenge), have been shown to causally affect disease development in rodents. They state that, although challenging, multi-omics approaches will provide crucial insight into the systemic role of intestinal microbiota and microbial metabolites in host metabolism. If causality can be demonstrated in humans, development of novel diagnostic and therapeutic tools that target the gut microbiota and/or its metabolites will have high potential.

Targeted next-generation sequencing reveals MODY in up to 6.5% of antibody-negative diabetes cases listed in the Norwegian Childhood Diabetes Registry

Bente B. Johansson, Henrik U. Irgens, Janne Molnes, Paweł Sztromwasser, Ingvild Aukrust, Petur B. Juliusson, Oddmund Søvik, Shawn Levy, Torild Skrivarhaug, Geir Joner, Anders Molven, Stefan Johansson, Pål R. Njølstad

MODY can mimic type 1 or type 2 diabetes. Correct identification of MODY is important for the improvement of diagnosis and management of diabetes. Many patients with a newly discovered MODY diagnosis can switch from insulin injections to oral glucose-lowering agents, thereby improving glucose control and achieving better quality of life. In this issue, Johansson et al describe the first nationwide systematic screening of MODY using next-generation sequencing. They show that the prevalence of MODY in antibody-negative childhood diabetes may reach 6.5% and that one-third of these individuals with MODY had not been recognised prior to the study. Since a correct diagnosis can lead to a change in treatment, the authors suggest that molecular screening of all antibody-negative children should be considered in routine diagnostics. This study is an example of how to implement precision medicine in diabetes clinics. This article is the subject of a commentary in this issue by Shields and Colclough.

Differential methylation of genes in individuals exposed to maternal diabetes in utero

Peng Chen, Paolo Piaggi, Michael Traurig, Clifton Bogardus, William C. Knowler, Leslie J. Baier, Robert L. Hanson

Individuals exposed to diabetes in utero (i.e. offspring whose mothers had diabetes during their pregnancy) are at high risk for developing type 2 diabetes and obesity. It has been proposed that epigenetic factors may be partly responsible for this risk, but there is a lack of identification of specific epigenetic changes that are associated with exposure to diabetes in utero. In this issue, Chen et al compare genome-wide DNA methylation profiles of Pima Indians exposed to diabetes in utero with those not exposed to diabetes in utero. They identify 39 separate genomic regions at which DNA methylation differed between the groups. At several of these regions, DNA methylation was also associated with obesity, impaired insulin secretion or risk of developing type 2 diabetes. Their findings suggest that intrauterine exposure to diabetes may influence epigenetic factors, such as DNA methylation, and that these epigenetic factors may influence metabolic processes that lead to type 2 diabetes.

Interferon-α mediates human beta cell HLA class I overexpression, endoplasmic reticulum stress and apoptosis, three hallmarks of early human type 1 diabetes

Laura Marroqui, Reinaldo S. Dos Santos, Anne Op de beeck, Alexandra Coomans de Brachène, Lorella Marselli, Piero Marchetti, Decio L. Eizirik

Three hallmarks of pancreatic islets in early human type 1 diabetes are overexpression of HLA class I, endoplasmic reticulum (ER) stress and beta cell apoptosis. Interferon-α (IFNα) is also expressed in human islets from individuals with type 1 diabetes and it is proposed that this cytokine is a common mediator of these three phenomena. In this issue, Marroqui et al report that IFNα induces hyperexpression of MHC class I proteins, inflammation and the ER stress response in human beta cells, sensitising these cells to another cytokine, IL-1β, leading to their death by apoptosis. These novel observations place IFNα as a central modulator of excessive inflammatory and ER stress responses in the early stages of type 1 diabetes, contributing to the progressive destruction of pancreatic beta cells and to the triggering of autoimmunity in genetically predisposed individuals. Hence, these findings suggest that targeting IFNα may be a promising adjuvant therapy in the early stages of type 1 diabetes.

Improved glycaemia in high-fat-fed neprilysin-deficient mice is associated with reduced DPP-4 activity and increased active GLP-1 levels

Joshua R. Willard, Breanne M. Barrow, Sakeneh Zraika

Neprilysin is a peptidase which, like dipeptidyl peptidase-4 (DPP-4), cleaves and inactivates glucagon-like peptide-1 (GLP-1). It is unknown whether, under conditions associated with type 2 diabetes (i.e. elevated glucose levels and high-fat-diet induced obesity), neprilysin deficiency enhances active GLP-1 and, thereby, improves blood glucose levels. In this issue, Willard, Barrow and Zraika report that neprilysin-deficient mice fed a high-fat diet exhibit increased active GLP-1 levels in plasma, as well as improved glucose tolerance, insulin sensitivity and beta cell function. Further, the authors observed that high-fat-fed neprilysin-deficient mice had reduced plasma DPP-4 activity. These findings suggest that neprilysin inhibitors may have clinical purpose for the treatment of type 2 diabetes.

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