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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 stand out in some regard and are very 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!

Hindrik Mulder, Editor

Lessons from single-cell RNA sequencing of human islets

Mtaki Ngara, Nils Wierup

Islet dysfunction is a key component of type 2 diabetes but due to the complex cell composition of the islets it has not been easy to understand how each of the five islet cell types is affected by or contributes to disease development. In this issue Ngara and Wierup (https://doi.org/10.1007/s00125-022-05699-1) summarise recent advances in islet biology enabled by single-cell RNA sequencing (scRNAseq). The authors discuss how scRNAseq has generated unprecedented insight into important aspects of islet biology, foremost by uncovering cell-type-specific gene expression in all islet cell populations. The technique has also proven highly useful in the stem cell and development fields. When it comes to identifying type 2 diabetes disease mechanisms, we have not yet seen a major breakthrough. However, the authors conclude that advances in computational methods in combination with larger studies will most likely lead to a leap forward in this area within the near future. The figure from this review is available as a downloadable slide.

Health impact of seven herpesviruses on (pre)diabetes incidence and HbA_{1c}: results from the KORA cohort

Tim Woelfle, Birgit Linkohr, Tim Waterboer, Barbara Thorand, Jochen Seissler, Marc Chadeau-Hyam, Annette Peters

During the COVID-19 pandemic, the link between viral infections and non-communicable diseases has once again become apparent. In this issue, Woelfle et al (https://doi.org/10.1007/s00125-022-05704-7) investigate the link between herpesvirus seroprevalence and the development of type 2 diabetes. The authors applied multiplex antibody assays and saw high co-occurrence of herpesviruses in this population-based study, where individuals exhibited antibodies against an average of four out of seven examined herpesviruses. Herpes simplex virus 2 increased the risk of (pre)diabetes incidence by more than 50% and cytomegalovirus by more than 30%. Many other factors such as age increase both the risk for viral infection and the risk for (pre)diabetes development. However, the authors report that the results were robust when they adjusted for potential confounders. The authors conclude that these findings highlight the need to better understand the link between asymptomatic viral infections and metabolic diseases and call for viral prevention strategies, potentially including the development of effective vaccines against herpesviruses.

Mediators of the association between educational attainment and type 2 diabetes mellitus: a two-step multivariable Mendelian randomisation study

Jia Zhang, Zekai Chen, Katri Pärna, Sander K. R. van Zon, Harold Snieder, Chris H. L. Thio

Higher educational attainment protects against type 2 diabetes, but the underlying mechanisms are uncertain. In this issue, Zhang et al (https://doi.org/10.1007/s00125-022-05705-6) report the results of a Mendelian randomisation study, in

which they used genetic instruments to minimise bias due to confounding. Using a multivariable extension of this method, they estimated mediation between educational attainment and type 2 diabetes by the modifiable risk factors BMI, sedentary behaviour, smoking and blood pressure. They estimate that up to 84% of the protective effect of higher educational attainment is mediated by lower levels of these risk factors. The two largest mediating factors were BMI and sedentary behaviour, each individually mediating 50% of the protective effect, with partially overlapping effects. The authors conclude that these findings might inform future trials and preventive policies to reduce the burden of type 2 diabetes due to educational inequalities.

Insulin-degrading enzyme ablation in mouse pancreatic alpha cells triggers cell proliferation, hyperplasia and glucagon secretion dysregulation

Beatriz Merino, Elena Casanueva-Álvarez, Iván Quesada, Carlos M. González-Casimiro, Cristina M. Fernández-Díaz, Tamara Postigo-Casado, Malcolm A. Leissring, Klaus H. Kaestner, Germán Perdomo, Irene Cózar-Castellano

Hyperglucagonaemia is a hallmark of type 2 diabetes, although its underlying mechanisms are poorly elucidated. Insulin-degrading enzyme (IDE) is a protease of insulin and glucagon which is highly expressed in human and mouse pancreatic alpha cells, although its expression levels are decreased in the pancreatic islet cells of individuals with type 2 diabetes. In this issue, Merino et al (https://doi.org/10.1007/s00125-022-05729-y) report that deletion of IDE in adult mouse alpha cells leads to increased proliferation, hyperplasia and constitutively elevated glucagon secretion, with lack of inhibition by insulin or high-glucose levels, leading to hyperglucagonaemia. Furthermore, they demonstrate that IDE deficiency triggers cytoskeletal perturbations, including increased α-synuclein aggregation and decreased tubulin levels, in parallel to impaired ciliogenesis in alpha cells. The authors conclude that these findings highlight novel molecular mechanisms of glucagon secretion regulation in pancreatic alpha cells, which may represent a future therapeutic target to treat hyperglucagonaemia in type 2 diabetes.

IgM-associated gut bacteria in obesity and type 2 diabetes in C57BL/6 mice and humans

James A. Pearson, Heyuan Ding, Changyun Hu, Jian Peng, Brittany Galuppo, F. Susan Wong, Sonia Caprio, Nicola Santoro, Li Wen

B cells secrete different immunoglobulins, which can target bacteria. IgA-deficiency promotes obesity through changes to the composition of gut bacteria; however, IgA deficiency often increases IgM. In this issue, Pearson, Ding and Hu et al (https://doi.org/10.1007/s00125-022-05711-8) used activation-induced cytidine deaminase (AID)-deficient mice (which produce only IgM) fed on a high fat diet to investigate the role of IgM in obesity. They show that increased IgM promoted weight gain and impaired glucose- and insulin tolerance by altering the composition of the intestinal bacteria in the mice. Administration of intravenous IgG, but not IgA, abolished the obesogenic profile of AID-deficient mice. The authors also showed that in obese children with impaired glucose tolerance and type 2 diabetes, IgM-bound stool bacteria are increased compared with normoglycaemic children without type 2 diabetes. Additionally, gut bacteria derived from either AID-deficient obese mice or obese children with impaired glucose tolerance and type 2 diabetes induced similar metabolic changes in germ-free mice. The authors conclude that these findings indicate that IgM may be important in the development of obesity and type 2 diabetes. All text supplied by the authors.