

# Diabetologia

## 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*

### **Maturation of beta cells: lessons from in vivo and in vitro models**

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*Tom Barsby, Timo Otonkoski*

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Many recent studies have uncovered novel molecular insights into the functional maturation of beta cells following postnatal development and throughout stem cell-derived islet differentiation. In this issue, Barsby and Otonkoski (<https://doi.org/10.1007/s00125-022-05672-y>) draw together recent findings in the regulatory and metabolic mechanisms underlying this maturation. The authors discuss how the interplay of nutrient sensitivity, metabolic signatures and circadian regulation are all important facets of functional maturation that regulate (and are regulated by) the transcriptomic state of the beta cell. This review further highlights that beta cell maturation is not a binary process and encompasses processes beyond the acquisition of a beta cell identity and the expression of a subset of particular single marker genes. The figures from this review are available as a downloadable [slideset](#).

### **Incidence of newly diagnosed diabetes after Covid-19**

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*Wolfgang Rathmann, Oliver Kuss, Karel Kostev*

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Inflammation caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may result in insulin resistance. It is unclear whether these metabolic changes are temporary, or

if coronavirus disease-2019 (Covid-19) may increase the risk of developing diabetes. In this issue, Rathmann et al (<https://doi.org/10.1007/s00125-022-05670-0>) report that adults who recovered from mild Covid-19 had a higher risk of developing type 2 diabetes than a matched control group who had other types of respiratory infections. New cases of type 2 diabetes were more common in individuals who tested positive for Covid-19 in primary care compared with those diagnosed with an acute upper respiratory infection (15.8 vs 12.3 per 1000 people per year, giving an incidence rate ratio of 1.28). The authors conclude that although type 2 diabetes is not likely to be a problem for the majority of people with mild Covid-19, anyone who has recovered from Covid-19 should be aware of symptoms such as fatigue, frequent urination and increased thirst, and promptly seek medical advice.

### **Young-onset diabetes in Asian Indians is associated with lower measured and genetically determined beta cell function**

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*Moneeza K. Siddiqui, Ranjit Mohan Anjana, Adem Y. Dawed, Cyrielle Martoeau, Sundararajan Srinivasan, Jebarani Saravanan, Sathish K. Madanagopal, Alasdair Taylor, Samira Bell, Abirami Veluchamy, Rajendra Pradeepa, Naveed Sattar, Radha Venkatesan, Colin N. A. Palmer, Ewan R. Pearson, Viswanathan Mohan*

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South Asians in general, and Asian Indians in particular, are at greater risk of early onset type 2 diabetes than white

Europeans. This contributes to the higher prevalence of diabetes in people of South Asian descent and the increasing burden of diabetes in South Asia. In this issue, Siddiqui and Anjana et al (<https://doi.org/10.1007/s00125-022-05671-z>) use data from non-migrant populations and show that the prevalence of lean young-onset type 2 diabetes is two to four times higher in Asian Indians compared with white Europeans. This phenotype highlights the potential role of poor insulin secretion due to impaired beta cell function in South Asians. The authors applied partitioned polygenic scores (pPS) for poor beta cell function to genetic data from India, Scotland and the UK Biobank, and report that South Asians have a greater genetic burden of beta cell dysfunction. They find that this genetic risk explains, in part, the higher risk of young-onset type 2 diabetes in lean South Asians. The authors conclude that these findings highlight the inter-ethnic differences in the genetics of diabetes and have implications for diabetes care for South Asians.

#### **XBPI maintains beta cell identity, represses beta-to-alpha cell transdifferentiation and protects against diabetic beta cell failure during metabolic stress in mice**

*Kailun Lee, Jeng Yie Chan, Cassandra Liang, Chi Kin Ip, Yan-Chuan Shi, Herbert Herzog, William E. Hughes, Mohammed Bensellam, Viviane Delghingaro-Augusto, Mark E. Koina, Christopher J. Nolan, D. Ross Laybutt*

Islet beta cell dedifferentiation has been implicated in beta cell failure in type 2 diabetes, although the mechanisms are poorly defined. The endoplasmic reticulum stress response factor X-box binding protein 1 (XBPI) is a major regulator of the unfolded protein response. Reduced XBPI expression has been observed in islets of people with type 2 diabetes. In this issue, Lee et al (<https://doi.org/10.1007/s00125-022-05669-7>) report that XBPI is crucial for the maintenance of beta cell identity and repression of beta-to-alpha transdifferentiation in mice. The authors show that deletion of *Xbp1* in adult mouse

beta cells deactivates beta cell identity genes and derepresses beta cell dedifferentiation and alpha cell genes. They also demonstrate that XBPI is required for beta cell compensation and protection against diabetes in insulin-resistant states. It is proposed that XBPI protects against beta cell apoptosis during metabolic stress by promoting the beta cell's antioxidant response. The authors conclude that targeting XBPI might help to reverse the process of beta cell dedifferentiation and restore functional beta cell mass in type 2 diabetes.

#### **Mucosal-associated invariant T cells are associated with insulin resistance in childhood obesity, and disrupt insulin signalling via IL-17**

*Ronan Bergin, David Kinlen, Nidhi Kedia-Mehta, Eadaoin Hayes, Féaron C. Cassidy, Declan Cody, Donal O'Shea, Andrew E. Hogan*

Insulin resistance is one of the first signs of metabolic dysregulation to manifest in childhood obesity, long before the development of overt metabolic disease. However, the primary drivers of insulin resistance in childhood obesity remain to be elucidated. In this issue, Bergin and Kinlen et al (<https://doi.org/10.1007/s00125-022-05682-w>) report that an innate T cell subset, the mucosal-associated invariant T (MAIT) cell, is strongly associated with insulin resistance in children with obesity. Furthermore, the authors demonstrate that the production of IL-17 by MAIT cells in particular is associated with insulin resistance. The authors then provide evidence from cell-based models that IL-17 can directly disrupt insulin-mediated glucose uptake. The authors conclude that these findings highlight a novel cellular driver of insulin resistance, which may represent a future therapeutic target.

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