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PANCREAS

Understanding nutrient-sensing at birth

At birth, mammals transition from an environment that provides a continuous supply of nutrients to conditions that are characterized by periods of fasting. This change requires many physiological adaptations, including the functional maturation of pancreatic β -cells, but the mechanisms behind these adaptations have remained unclear. Now, in a new study, David Sabatini and Douglas Melton provide insight on the environmental signals that govern this process.

“Although in the lab we can produce millions of cells that highly resemble native β -cells, these stem cell-derived β -cells don’t secrete insulin as well as real β -cells in response to glucose,” expounds Douglas Melton, co-corresponding author on the study. “We therefore wanted to better understand how β -cells become functional after birth and try to mimic this transition.”

The researchers measured metabolite profiles in fetal and neonatal mouse blood. They observed that embryonic mice have higher serum amino acid and lower glucose levels than mice that are a week old and that embryonic islets secrete insulin in response to amino acids while adult islets gain responsiveness to glucose.

To understand the underlying mechanisms, the team examined the activity of the nutrient-sensing mTORC1 pathway. “In fetal β -cells the mTORC1 pathway is sensitive to amino acids, whereas in maturing β -cells the pathway becomes sensitive to glucose as well,” says Andrew Cangelosi, co-first author of the study.

The researchers observed that pluripotent stem cell-derived β -cells, just like fetal-derived β -cells, have a limited ability to activate mTORC1 in response to glucose. However, the cells could be induced to mature by exposing them to an adult or ‘adult-like’ nutrient environment. “Environmental nutrients are sensed by the mTORC1 pathway and contribute to cell maturation,” explains Sabatini.

These data could aid research in regenerative medicine. “Our work suggests that researchers can exploit nutrients and nutrient sensing to improve the functional maturation of stem cell-derived β -cells in vitro,” concludes co-first author Ronny Helman.

More work remains to be done to determine the role other nutrients and metabolites might have in regulating β -cell maturation.

Anna Kriebs, Associate Editor,
Nature Communications

ORIGINAL ARTICLE Helman, A. et al. A nutrient-sensing transition at birth triggers glucose-responsive insulin secretion. *Cell Metab.* 31, 1004–1016 (2020)

NEUROENDOCRINOLOGY

Sweet signals — gut–brain circuit for sugar identified

The connection between the activation of sweet taste receptors on the tongue and the brain was defined in the early 2000s. Since the original investigations, however, researchers have been unable to explain why animals that lacked sweet receptors on the tongue still acquire a preference for sugar. Furthermore, it has remained unclear why artificial sweeteners, which activate the same sweet taste receptor on the tongue as sugar, do not generate the same behavioural preference as sugar.

Now, a new study published in *Nature* has shown that glucose activates a gut–brain neural circuit that communicates the presence of sugar to the brain. “When we were examining animals that lacked sweet receptors, and therefore were ‘blind’ to presence of sugar, we, and others, made an unexpected observation — even though the

animals could not taste sugar they eventually learned to recognize the bottle containing sugar,” explains Hwei Ee Tan, co-lead author on the study. “In the present study we set about identifying the brain circuits responsible for mediating sugar preference, independent of the taste system.”

The authors started by searching for areas of the brain that were activated by sugar in wild-type versus sweet receptor-deficient animals and then sought to identify the origin of these signals. The team found that the desire for sugar is mediated by a selective circuit from the gut to the brain. This novel pathway is distinct from the taste circuits that operate from the tongue to the brain, which mediate the ‘liking’ for sugar.

“We also demonstrated that silencing this circuit completely prevented the development of sugar

DIABETES

Role of long non-coding RNA in T1DM

The precise mechanism that initiates the autoimmune response that leads to type 1 diabetes mellitus (T1DM) is unknown. Many of the genetic associations that have been identified so far are in non-coding regions of the genome; however, their contribution to T1DM pathogenesis has not been studied in detail. A new study has now characterized a long non-coding RNA (lncRNA) that is associated with T1DM.

The researchers focused on alleles of *Lnc13*, which has previously been associated with T1DM. They used a range of techniques to characterize the lncRNA in vitro. “Moreover, we have also analysed human pancreatic islets to confirm our in vitro results and to determine the impact of a T1DM-associated SNP in *Lnc13* in the activation of the inflammatory process,” explain corresponding authors Izortze Santin and Ainara Castellanos-Rubio. “For this purpose,

an overexpression vector for *Lnc13* harbouring each of the alleles was generated and used throughout the study to test not only downstream effects, but also differential binding of each of the lncRNA forms to the interacting PCBP2 protein and *STAT1* mRNA.”

Santin, Castellanos-Rubio and colleagues found that *STAT1* expression was increased in human pancreatic islets that had the T1DM-associated *Lnc13* risk genotype rs917997*CC compared with islets that had the heterozygous genotype rs917997*CT. Thus, activation of the *STAT1* proinflammatory pathway was increased in islets with the risk genotype. “Activation of this pathway in β -cells facilitates the generation of the proinflammatory environment (insulinitis) observed in the initial stages of T1DM pathogenesis, and thus, the impact of *Lnc13* in this process might be crucial