Credit: tiripero/Getty

METABOLISM

T cells in gut linked to metabolism

The pathways that govern how our bodies process and use the nutrients we ingest are tightly regulated to ensure our metabolic needs are met. A new study published in *Nature* describes how a subset of immune cells named integrin β7$^+$ natural gut intraepithelial T lymphocytes (IELs), which are dispersed throughout the small intestine, modulate systemic metabolism.

"We were initially interested in a completely different question; we wanted to know whether leukocytes pick up cholesterol in the gut and bring it — like Trojan Horses — to growing atherosclerotic lesions," explains corresponding author Filip Swirski. "However, because β7 is an integrin that guides leukocyte recruitment to the gut, it made sense to look at integrin β7-knockout mice." Swirski and his team found that integrin β7-knockout mice have heightened metabolism, which led the team to alter their hypothesis.

Following the discovery that integrin β7-knockout mice have a different metabolic output compared with wild-type mice, the investigators aimed to uncover the cells that account for these differences and the mechanisms involved. The team focused their efforts on immune cells in the small intestine, as integrin β7 guides leukocytes to the gut. "After eliminating B cells and myeloid cells, we noticed that the metabolic phenotype of β7-knockout mice depended on T cells or more specifically, depended on IELs," adds Swirski.

The authors then set about uncovering the mechanisms responsible for the metabolic differences. Swirski and his team found that glucagon-like peptide 1 (GLP1) had a pivotal role. "GLP1, which is produced in the gut, has many endocrine functions, not the least of which is to alert the pancreas to produce insulin," explains Swirski. The investigators discovered that mice lacking integrin β7 have increased levels of GLP1 in the circulation compared with wild-type mice. "These data, combined with the observation that IELs express the GLP1 receptor, led us to investigate whether IELs regulate GLP1 bioavailability and this turned out to be the case," adds Swirski.

The authors now want to investigate the questions this study has raised. "We still need to know precisely how IELs regulate GLP1 bioavailability, as well as whether and how IELs change over the course of life, or even over the course of a day," adds Swirski. The authors also plan to investigate how their findings relate to humans. For example, it might be possible to control the number of IELs and/or their function to treat obesity, diabetes mellitus, cardiovascular or other diseases.

Alan Morris

ORIGINAL ARTICLE He, S. et al. Gut intraepithelial T cells calibrate metabolism and accelerate cardiovascular disease. *Nature* **566**, 115–119 (2019)

PANCREAS

Imaging β-cell function in vivo

In live animals, non-invasive imaging of β-cell function has previously not been achieved owing to substantial technical challenges. A study published in *eLife* used a newly developed high-resolution two-photon light-sheet microscope (2P3A-DSLM) for the first in vivo imaging of β-cell function and development in transgenic embryonic zebrafish.

Insulin secretion is triggered from β-cells by a glucose-induced influx of Ca^{2+}, which serves as a functional marker. The new microscopy technique was able to visualize Ca^{2+} flux in response to glucose in every single β-cell present in transparent transgenic embryonic zebrafish, which were engineered to have β-cells labelled with a fluorescent Ca^{2+} indicator.

Interestingly, the researchers observed two waves of β-cell functionality that propagated from the islet mantle to the core during zebrafish development. Visualization of blood vessels indicated that the acquisition of β-cell functionality was coordinated by islet vascularization, which was required for the delivery of optimal glucose concentrations.

Calcineurin–nuclear factor of activated T cells (NFAT) signalling is thought to have a role in β-cell function in mice. Glucose-induced Ca^{2+} influx in β-cells was analysed in zebrafish embryos that were preincubated with calcineurin–NFAT inhibitors or activators. These experiments showed that calcineurin–NFAT signalling acts downstream of glucose to induce β-cell functionality.

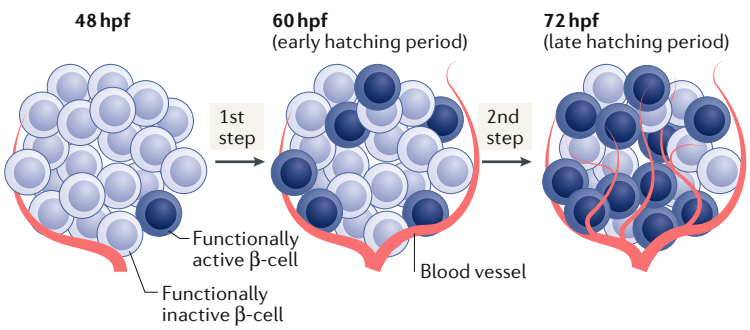
Importantly, these findings could be partially replicated in mammals. In ex vivo embryonic mouse islets, direct activation of calcineurin induced secretion of insulin in response to stimulation with a high, but not a low, concentration of glucose.

"The calcineurin–NFAT signalling pathway has never been directly manipulated in the differentiation of stem cells into functionally mature β-cells in vitro," explain corresponding authors Liangyi Chen and Yanmei Liu. "Only by imaging the spatiotemporal profile of β-cell functional acquisition in vivo, we highlighted that this pathway is a maturation factor that was previously overlooked."

This study presents the first imaging of the functionality of individual β-cells in live animals and reveals important biology. "We plan to use these findings to generate matured β-cells derived from stem cells in vitro, which will be important for β-cell regenerative approaches for diabetes therapy," conclude Chen and Liu. "In the meantime, we will continue screening new compounds that promote β-cell maturation by using the transgenic zebrafish model developed in this study."

Shimona Starling

ORIGINAL ARTICLE Zhao, J. et al. In vivo imaging of β-cell function reveals glucose-mediated heterogeneity of β-cell functional development. *eLife* **8**, e41540 (2019)



In embryonic zebrafish pancreatic islets, the acquisition of β-cell functionality is coordinated by islet vascularization. hpf, hours post-fertilization.