NEWS

Advances in GDF15 research

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GDF15, which is expressed in a variety of tissues, is currently being investigated as a potential target for therapies that target obesity. Now, two papers have furthered our understanding of GDF15 by elucidating its role in feeding and emesis behaviours and by highlighting it as a potential target for the treatment of type 1 diabetes mellitus (T1DM).

In the first of the two papers, Bart De Jonghe and colleagues investigated the role of GDF15 in feeding and emesis behaviours. The team's investigation followed a group of papers that were simultaneously published in *Nature Medicine* in September 2017. “The *Nature Medicine* papers identified the GDF15 receptor as GFRAL and showed that it was almost exclusively located within the brainstem, which is where several classical neuronal hubs of emetic and feeding behaviour reside,” explains De Jonghe. “These data provided a strong reasoning to examine the role of GDF15 in nausea and emetic circuitry.”

The team used three animal models, namely rats, mice and shrews, to study nausea behaviours following treatment with GDF15. “All animals have species-specific nausea behaviours, so it is crucial to use multiple models and gain

confidence in understanding how nausea can manifest within each to arrive at any sort of convincing conclusion,” adds De Jonghe.

The investigators found that GDF15-induced reductions in food intake are accompanied by an increase in measures of nausea. These data have implications for the development and tolerance of a GDF15-based ligand for the treatment of obesity. “The converse, however, is that there is promise for GDF15-based antagonists or antibodies not only in anti-cachexia, but as an anti-nausea and/or anti-emetic class of drugs,” explains De Jonghe. “The latter is desperately needed, as despite a large array of commercially available anti-emetics, nausea and vomiting are still omnipresent clinically.” De Jonghe and colleagues plan to follow up on these data and explore the potential of pharmacotherapies targeted at GDF15–GFRAL inhibition as treatments of nausea and cachexia.

In the second study, Thomas Metz and colleagues found that GDF15 expression is downregulated in isolated human islets following treatment with pro-inflammatory cytokines to initiate islet stress. “In the present study we sought to apply omics techniques (such as proteomics and metabolomics) to the analysis of human islets in order to identify novel biomarkers of stress and dysfunction that might be indicative of β -cell loss,” adds Metz.

The team performed molecular profiling, including proteomics analysis, on isolated human islets following treatment with inflammatory cytokines to identify the proteins that were altered. “Our hypothesis was that these comprehensive analyses could identify the cellular and signalling pathways that are regulated as part

of the islet response,” explains Metz. “The proteins within these pathways might represent new targets for therapeutic intervention or be novel biomarkers of islet stress and β -cell death that could be monitored by blood screening.”

Metz and colleagues found that 3% of the measurable islet proteome was altered following cytokine treatment. Approximately two thirds of these proteins were upregulated, but most intriguingly, of the one third of proteins that were downregulated, the team identified three growth factors, one of which was GDF15. Owing to correlations between its downregulation with islet stress and apoptosis, the investigators hypothesized that GDF15 could be a protective factor. “This hypothesis was supported by the observation of reduced levels of GDF15 expression in pancreata of individuals with T1DM when compared with either healthy controls or individuals with T2DM,” says Metz.

Following the omics studies, the team isolated human islets and human β -cells with recombinant GDF15. Pre-treatment with recombinant GDF15 rescued both β -cells and isolated human islets from cytokine-induced apoptosis. “Further to these data, we showed that treatment of non-obese diabetic mice with recombinant GDF15 reduced both the incidence of insulinitis and T1DM by over 50%,” adds Metz.

The team plan to continue their work on GDF15, with the primary goal of elucidating the mechanisms by which it is downregulated in stressed islets and the way in which it confers protection against inflammation and apoptosis in human islets and β -cells.

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ORIGINAL ARTICLES Borner, T. et al. GDF15 induces anorexia through nausea and emesis. *Cell Metab.* <https://doi.org/10.1016/j.cmet.2019.12.004> (2020) | Nakayasu, E. S. et al. Comprehensive Proteomics analysis of stressed human islets identifies gdf15 as a target for type 1 diabetes intervention. *Cell Metab.* <https://doi.org/10.1016/j.cmet.2019.12.005> (2020)

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