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Microbial Metabolite UDP-Galactose Restores Islet β-cell Function in Mice via the Gut–Islet Axis

Author: Feng Zhang, PhD

Affiliation: Hospital of Jiangnan University

Abstract: The gut–islet axis, linking the gut microbiota and pancreatic islet β-cells, has expanded our understanding of the progression of diabetes.

However, to date, few suitable targets in the gut–islet axis have been shown to effectively promote β-cell function. This study identified a new top-down pathway of the gut–islet axis that promotes the reprogramming of pancreatic islet cells into mature β-cells following insulin treatment, which is mediated by the microbial metabolite uridine diphosphate galactose (UDP-gal). This bioactive compound selectively bound to purinergic receptor P2Y, G-protein coupled, 14 (P2ry14) and activated the MEK-

ERK pathway in islets, thereby promoting β-cell reprogramming. Furthermore, UDP-gal injection was found to directly promote β-cell reprogramming and this effect could be reversed by the inhibition of

P2ry14, suggesting that microbial UDP-gal could be used as a key mediator of the gut–islet axis to promote β-cell differentiation.

Key words: insulin therapy; Microbial metabolite; UDP-gal; β-cell function; gut microbiota; Gut-islet axis