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Control of intestinal stem cell fate: A novel approach to treating diabetes

Gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are incretins released from enteroendocrine cells into the circulation in response to ingested nutrients, such as glucose and fat. GIP is secreted from K-cells in the duodenum and upper small intestine, and GLP-1 is secreted by L-cells in the lower small intestine and colon. In addition to its glucose-dependent insulinotropic effect, GLP-1 has other beneficial effects that help achieve targeted blood glucose levels, such as inhibition of glucagon secretion, delayed gastric emptying and appetite suppression¹. However, both GLP-1 and GIP are rapidly degraded and inactivated *in vivo* by dipeptidyl peptidase-4 (DPP-4). Two methodologies have been developed to enhance the incretin effect as therapy for diabetes, DPP-4 inhibitors and GLP-1 receptor agonists resistant to cleavage by DPP-4.

Another possible approach is enhancement of endogenous GLP-1 secretion. Severely obese patients with type 2 diabetes who undergo bariatric surgery show significant and rapid improvement of glycemic control even up to complete cure of diabetes. The underlying mechanism of the dramatic improvement in glycemic control observed in these patients seems partly independent of weight reduction, and is associated with alterations in the secretion of enteroendocrine hormones, such as increased plasma levels of GLP-1. As endogenous GLP-1 concentrations are remarkably increased 5–10-fold after bariatric surgery², the therapeutic potential of enhancing endogenous GLP-1 secretion

is strongly suggested. However, no ideal strategy to stimulate GLP-1 secretion has been reported. Recently, Petersen *et al.*³ showed that blocking the NOTCH signaling pathway with γ -secretase inhibitor in mouse and human intestinal organoids increased the number of L-cells, and augmented glucose-stimulated GLP-1 secretion. Furthermore, in high-fat diet-fed mice with impaired glucose tolerance, administration of γ -secretase inhibitor improved the early insulin response to glucose, and restored glucose tolerance in association with a significant increase in L-cell number and GLP-1 secretion.

Enteroendocrine cells arise from pluripotent intestinal stem cells located in intestinal crypts (Figure 1). The earliest cell fate decisions are regulated by the NOTCH signaling pathway⁴. When membrane-bound NOTCH receptor interacts with ligand anchored in the membrane of neighboring cells, an intrinsic γ -secretase cleaves the receptor, releasing the NOTCH intracellular domain (NICD). NICD translocates into the nucleus, and stimulates the expression of hairy and enhancer of split 1. Hairy and enhancer of split 1 has been shown to repress expression of protein atonal homolog 1 and neurogenin 3. Atonal homolog 1 is the first factor known to be involved in endocrine specification, inducing cells to the secretory lineages, goblet, paneth and enteroendocrine cells. Neurogenin 3 is expressed in the precursor cell to all enteroendocrine cells, and loss of neurogenin 3 in mice results in a loss of most enteroendocrine lineages. Thus, activation of NOTCH signaling induces intestinal stem cells to differentiate into absorptive epithelial cells, and blocking the NOTCH signaling pathway increases the number of cells differentiating into

enteroendocrine lineages including L-cells.

L-cells secrete not only GLP-1, but also oxyntomodulin and peptide YY, anorexic hormones known to be involved in food intake, energy expenditure and regulation of glucose homeostasis. Therefore, enrichment of L-cells might increase these anorexic hormones, resulting in appetite suppression and reduction in bodyweight. However, repetitive treatment with NOTCH inhibitor is toxic and not suitable for continuous use to reduce bodyweight.

Gamma-secretase inhibitor was found to increase the number not only of L-cells, but also of K-cells, which resulted in increased GIP secretion. GIP has been explored as a potential glucose-lowering drug based on its glucose-dependent insulinotropic effect. It has been reported that the insulinotropic action of GIP is impaired in diabetic patients and is ameliorated as the glycemic condition is improved⁵. Thus, GIP will have synergistic effects with augmented GLP-1 signaling after treatment with NOTCH inhibitor. In contrast, studies of GIP receptor knockout mice describe GIP as an obesity-promoting factor in high-fat diet conditions, and show that deletion of GIP receptor signaling causes resistance to diet-induced obesity⁶. Additionally, partial reduction of GIP alleviates obesity, and lessens the degree of insulin resistance without exacerbating glucose tolerance under high-fat diet conditions⁷. These findings suggest that regulation of GIP secretion, especially after fat intake, is a promising therapeutic approach to obesity and type 2 diabetes, and GIP antagonists have been proposed to improve insulin sensitivity by preventing the development of obesity. Because GIP exhibits not only an insulinotropic effect, but also an obesity-promoting effect, it is still controversial whether or

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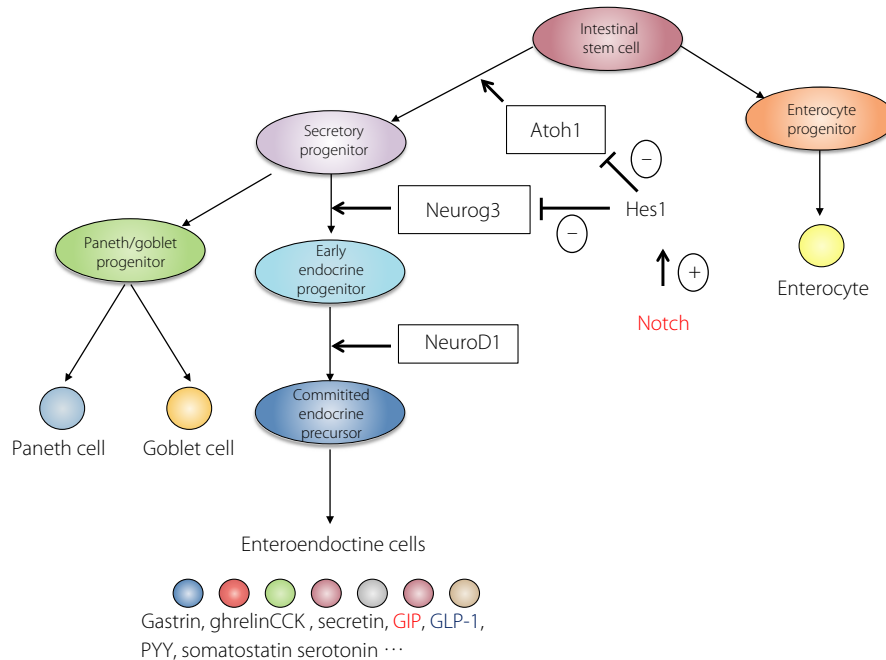


Figure 1 | Schematic overview of enteroendocrine differentiation. Pluripotent intestinal stem cells located in intestinal crypts differentiate into all four cell types present in the intestinal epithelium. NOTCH signaling promotes differentiation to the absorptive lineage by repressing protein atonal homolog 1 (Atoh1) transcription. Atoh1 restricts cells to the secretory subset and neurogenic differentiation 1 restricts cells to the endocrine lineage. CCK, cholecystokinin; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; Hes1, hairy and enhancer of split 1; NeuroD1, neurogenic differentiation 1; Neurog3, neurogenin 3; PYY, peptide YY.

not enhanced GIP secretion after treatment with NOTCH inhibitor contributes to the improvement of metabolic conditions, especially under high-fat diet feeding.

The effect of NOTCH inhibition is not selective for only L-cells and K-cells; other enteroendocrine hormones might also be increased, such as ghrelin, a representative orexigenic hormone, and gastrin, which stimulates gastric acid secretion. It is therefore possible that increased appetite, intractable peptic ulcer disease and other adverse reactions could occur as a result of increased enteroendocrine cells using NOTCH inhibitor clinically. Regarding the effects of NOTCH inhibition on pancreatic β -cells, Petersen *et al.*³ showed that treatment with NOTCH inhibitor for two consecutive days had no direct effects on insulin secretion, and that increased insulin secretion and improved glucose tolerance were mainly a result of augmented GLP-1 release in NOTCH inhibitor-treated mice. Previously, *in vitro*

analysis has shown that inhibition of NOTCH signaling promotes differentiation of embryonic pancreatic cells into functional islet-like clusters and induces dedifferentiated β -cell-derived cells into redifferentiated, functional β -cells⁸. There is as yet no demonstration of the effects of long-term inhibition of NOTCH signaling on islet morphology and function *in vivo*, which is a critical issue to be clarified in the future.

NOTCH signaling plays an important role in original development and determination of cell fate, and it is deregulated in not only hematological malignancies, but also in solid tumors⁹. Targeting of the NOTCH signaling pathway as a treatment for cancer is currently under development. However, clinical development has stagnated due to treatment-related toxicities, especially gastrointestinal adverse events, and by necessarily complex optimizing processes for drug dosing schedules. In such conditions, NOTCH inhibitors may well not be available for

clinical application for the treatment of diabetes in the near future. Identification of a more selective regulator of L-cell development should be prioritized for clinical application. Nevertheless, targeting L-cell development and enrichment of incretin-secreting cells could potentially evolve as novel, effective therapeutics for diabetes.

DISCLOSURE

Nobuya Inagaki served as a medical advisor for Takeda, Taisho Pharmaceutical, GlaxoSmithKline and Mitsubishi Tanabe Pharma, and lectured for MSD, Sanofi, Novartis Pharma, Dainippon Sumitomo Pharma, Kyowa Kirin and Mitsubishi Tanabe Pharma, and received payment for services. Shunsuke Yamane declares no conflict of interest.

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