Diabetes & Metabolism 45 (2019) 601–602

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Letters to the editor

Glucagon-like peptide-1 promotes α-to-β cell transdifferentiation: How far is it from clinical application?

ARTICLE INFO

Keywords:
Glucagon-like peptide-1
Cell transdifferentiation
β cell regeneration
Snacking

Glucagon-like peptide-1 (GLP-1)-based therapies, including GLP-1 analogs and dipeptidyl peptidase-4 (DPP-4) inhibitors, have gained widespread usage for the treatment of type 2 diabetes (T2D). Clinical trials show that GLP-1 analogs as a treatment option for T2D alone or in combination with other anti-diabetic agents can improve glycaemic control and reduce body weight with low risk of hypoglycaemia. Moreover, preclinical studies provide various evidences of β cell-protective actions. In the December issue of Diabetes 2018, Lee et al. [1] reported for the first time that GLP-1 increased β cell regeneration by promoting α-to-β cell transdifferentiation.

Recently, transdifferentiation of non-β cells into β cells has attracted much attention. Various cells from different tissues have been successfully reprogrammed into functional β cells [2]. Among them, α cells are an attractive source (summarized in [2]). Extreme conditions, gene manipulations, epigenetic modifications, and small molecule interventions have been reported to convert α cells into β cells. However, gene manipulations cannot be used for clinical applications because the viral vector can be integrated into the host genome, which may result in tumorigenesis. Epigenetic modifications cannot induce complete cell phenotype conversion, and the obtained β cells are not fully functional. Studies from small molecules displayed paradoxical results [3]. Lee's article showed that GLP-1 promoted α-to-β cell transdifferentiation. Although adenovirus was used in his article, GLP-1-based therapies or other anti-diabetic therapies that upregulate GLP-1 level (e.g., glucagon receptor blockage) might hold the potential to transdifferentiate α cells into β cells.

In addition to the gene manipulation and risk of viral integration into the genome and carcinogenesis, some other questions also require attention according to Lee's study. The rAd-*GLP-1* upregulated the circulating GLP-1 level as early as the first 2 days, and was 25-fold higher than the physiological level at the first week and maintained the high level for at least 4 weeks (2-fold higher at week 4). By contrast, GLP-1 analogs achieve a 10-fold increase, while DPP-4 inhibitors cause a 2-fold increase in plasma GLP-1 [4]. Does GLP-1 at such levels have the capacity to promote cell transdifferentiation? If not, the safety of high levels of GLP-1 must be evaluated. DPP-4 is also produced in the islet (exclusively α cells in human and predominantly β cells in mice) [5], and its physiological function there is to regulate the amount of GLP-1. GLP-1 production is low, and its degradation by DPP-4 is rapid in healthy individuals without metabolic syndrome. GLP-1 levels decrease in T2D individuals, while DPP-4 activity is significantly lower in islets from T2D donors than in non-diabetic donors [5]. Therefore, whether such a supra-physiologically high level of GLP-1 in Lee's paper is safe or not must be clarified.

Humans and mice have different repair and compensatory mechanisms of islets and have different responses to GLP-1. GLP-1 directly induced proliferation of β cells in rodents, while β cell replication was not detected in human islets even when exposed to high concentrations of GLP-1 [6]. Unsurprisingly, GLP-1 may have different effects on α cells between humans and mice. Nevertheless, it is difficult to obtain human pancreatic donors with GLP-1 treatment.

As mentioned above, GLP-1 is rapidly degraded by the ubiquitous DPP-4. Although the high level of GLP-1 in circulation may have beneficial effects on islets, the upregulated GLP-1 level in the islet microenvironment is even more important. A recent study has verified that the pancreas but not the gut mediates the GLP-1-induced glucoincretin effect [7]. Lee's study found that rAd-*GLP-1* enhanced the secretion of GLP-1 in islet cells. Maybe intra-islet GLP-1 rather than systemic GLP-1 plays pivotal roles during cell phenotype conversion.

Lee's study demonstrated that the increased α cell mass was derived from cell proliferation. Under several conditions, however, the increased α cells also derived from pancreatic endocrine progenitors. For instance, when *Pax4* was overexpressed or *Arx* was deleted in α cells, α cells were pushed to convert into β cells, and then pancreatic endocrine progenitors in the ductal region were activated and differentiated into α cells [2]. The inducible endocrine progenitor lineage-tracing mice confirmed this conclusion. Butler et al. [8] carried out a histological study in the human pancreas of organ donors with T2D treated with incretin. They found that α cell mass was enlarged, and the increased α cells were within the duct itself or in the immediate peri-ductal location, suggesting that α cells might be derived from the progenitors. Differences between Lee's and Butler's results may be because of the diverse GLP-1 levels in the circulation or may be due to the different characteristics of humans and mice.

Lee's study also displayed that *FGF21* knockout or knockdown inhibited the GLP-1-induced transdifferentiation, but not completely. Both the GLP-1 analog exendin-4 and FGF21 increased insulin$^+$glucagon$^+$ or Pdx1$^+$glucagon$^+$ cell numbers and upregulated Pdx1 expression in streptozotocin (STZ)-treated islets. However, GLP-1 upregulated or maintained glucagon expression on day 3 or 7, while FGF21 downregulated glucagon expression. The inconsistency suggested that the effects of GLP-1 on cell transdifferentiation might be only partially mediated via FGF21. The other mechanism needs to be clarified. FGF21-based therapies are being developed for

https://doi.org/10.1016/j.diabet.2019.01.003

the treatment of metabolic disorders, including diabetes. Therefore, it is interesting to see if FGF21 has the potential to promote α-to-β cell transdifferentiation in patients with diabetes.

Finally, GLP-1 "promotes" rather than "initiates" β cell regeneration, because in the STZ-induced diabetic mice without rAd-*GLP-1*, there are also insulin^{+}glucagon^{+} bihormonal cells or Pdx1^{+}glucagon^{+} double-labeling cells. The mechanism of α-to-β cell transdifferentiation and the mechanism of the promoting effects of GLP-1 need to be further investigated. Additionally, Lee's study was performed in an STZ-induced model of type 1 diabetes (T1D). In this condition, the residual β cells are merely preserved. We are eager to know whether GLP-1 promotes α-to-β cell conversion in other T1D (e.g., NOD mice) or T2D models.

In summary, GLP-1 at a supra-physiological or even supra-pharmacological level enhances β cell regeneration through promoting α-to-β cell transdifferentiation. However, the mechanism requires further verification, and the clinical implication should be cautiously evaluated.

Disclosure of interest

The authors declare that they have no competing interest.

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Received 28 November 2018
Available online 17 January 2019