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Transdifferentiation of α- to β-cells is Enhanced in FSTL3 KO Mice

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Comments
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Transdifferentiation of α- to β-cells is enhanced in FSTL3 KO mice.

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Both type 1 and type 2 diabetes involve loss of functional pancreatic β-cells which is driving research into potential replacement sources. Expansion of functional β-cell mass, such as through induction of β-cell neogenesis or through transdifferentiation of α-cells into functional β-cells represent appealing therapeutic solutions to restoring glucose control. To date, however, these processes have been induced through genetic manipulation or severe pancreatic injury. It remains to be determined whether transdifferentiation or neogenesis contribute to functional β-cell mass under normal physiological conditions and/or contribute to β-cell expansion and how these processes are regulated.

We have reported that inactivation of the activin antagonist follistatin like-3 (FSTL3) resulted in a 2-fold increase in mean islet size with an enlarged β-cell component. We hypothesized that the β-cell expansion resulted from accelerated α- to β-cell transdifferentiation that was induced by the enhanced activin bioavailability of the FSTL3 KO mouse. We first demonstrated that activin suppressed important α-cell gene expression and promoted β-cell gene expression in α- and β-cell lines. We then used cell sorting based on natural fluorescence of α- and β-cells to achieve >95% enrichment of these cell populations. Activin treatment of these primary cells also suppressed α-cell gene expression including ARX. To explore whether activin had this effect in vivo, we used lineage tracing to label α-cells with YFP using Gluc-Cre/YFP mice crossed with FSTL3 KO mice. Cell sorting identified 2 additional populations, YFP labeled α-cells and YFP labeled β-cells with the number of YFP+Ins+ cells increased in FSTL3 KO islets compared to WT. These results suggest that α- to β-cell transdifferentiation occurs in the absence of genetic drivers or injury, that this process is increased in FSTL3 KO mice, and that activin may promote transdifferentiation to increase β-cell mass. Supported by JDRF (17-2012-414)