

P004 *Myt1* and *Ngn3* form a feed forward expression loop to regulate endocrine differentiation

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Ngn3 is a key intrinsic regulator of islet cell differentiation in pancreatic endoderm. *Ngn3*⁺ cells in the developing pancreas rapidly activate a group of transcription factors to initiate endocrine differentiation, underlining the importance of *Ngn3* expression regulation. Several factors are known to regulate the expression of *Ngn3*, including *Ngn3* itself, as well as multiple signals from adjacent cells and tissues including Notch signals. Here we report that a zinc finger transcription factor *Myt1*(*Nzf2*) and *Ngn3* form a feed-forward expression loop to regulate endocrine differentiation. Specifically, *Myt1* induces glucagon expression through activating *Ngn3* in pancreatic progenitors. Vice versa, *Ngn3* expression also induces the expression of *Myt1*. Consistent with this positive feed-forward regulation mechanism, *Myt1* expression largely, but not solely, depends on the presence of *Ngn3* in the pancreas. Furthermore, glucagon-expressing endocrine cells are found in *Ngn3* nullizygous mutant pancreas, and most of these cells maintain *Myt1* expression. These results suggest that *Myt1* and *Ngn3* positively regulate the expression of each other and consequently guide endocrine differentiation. In addition, the data uncovered an unexpected *Ngn3*-independent endocrine cell production pathway, which further bolts the notion that the seemingly equivalent endocrine cells of each type are heterogeneous in their origin.