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Phenotypic plasticity in the pancreas: new triggers, new players

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The pancreas has a very limited regenerative potential during homeostasis. Despite its quiescent nature, recent *in vivo* models suggest a certain degree of regeneration and cellular interconversion is possible within the adult pancreas. It has now become evident that cellular plasticity can be observed in essentially all cell types within the pancreas when provided with the right stress stimuli.In this review, we will focus on the latest findings uncovering phenotypic plasticity of different cell types in the pancreas, the molecular mechanisms behind such plasticity and how plasticity associated with pancreatic or non-pancreatic cells could be harnessed in the generation of new insulin-producing beta cells.

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Introduction

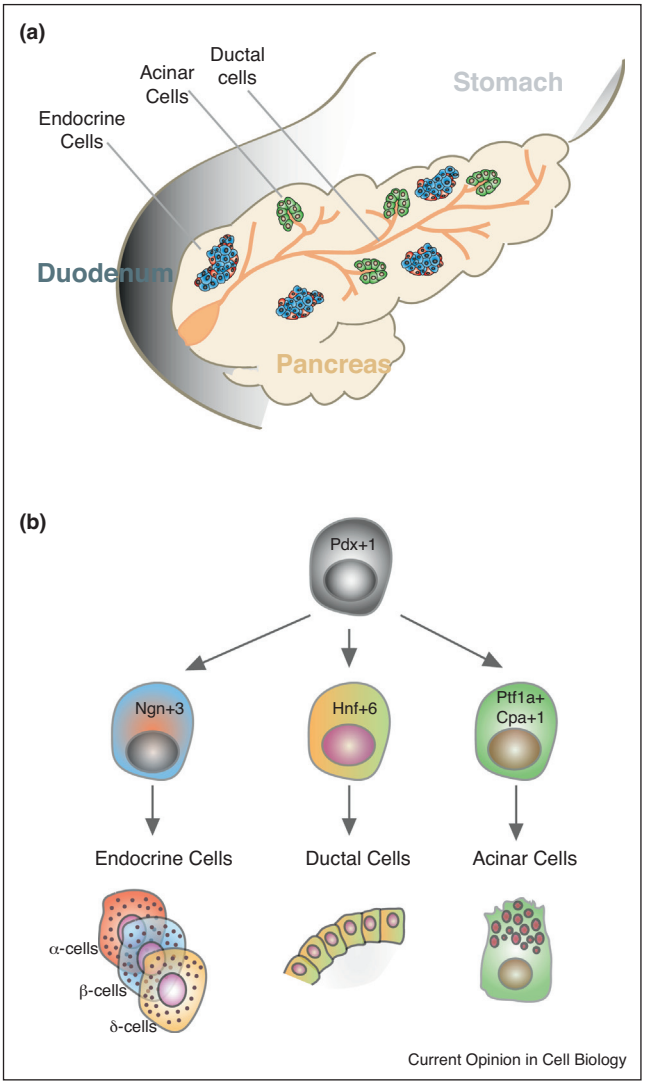
The precise control of tissue homeostasis is essential for multicellular organisms. Tissue homeostasis maintenance has been classically attributed to proliferation of terminally differentiated cells and to differentiation of dedicated adult stem cells. However, it has now become clear that cell plasticity is an additional player in tissue homeostasis, especially after injury [1]. Cell plasticity — that is, the ability of one cell type to convert into another by lineage reversion (dedifferentiation) or direct differentiation (transdifferentiation) — has been extensively observed in highly dynamic tissues such as skin and intestine [2]. Conversely, observing cellular plasticity events in less active tissues, such as the pancreas, has been more challenging.

In sharp contrast to the dynamism of epidermal and intestinal cells, pancreatic cells do not regenerate continuously. The pancreas is a mixed gland composed of exocrine (ductal and acinar cell) and endocrine (alpha, beta, pp, delta and epsilon cell) parts. Exocrine cells fulfil digestive functions. Acinar cells specialise in producing and releasing enzymes that are guided to the duodenum through a network formed by ductal cells. Endocrine cells, physically confined to the islets of Langerhans, regulate glucose metabolism by secreting different hormones to the bloodstream. Insulin (from beta cells), glucagon (from alpha cells) and somatostatin (from delta cells) are essential hormones produced in the pancreatic islets (Figure 1a) [3]. Loss of beta cells in type-1 diabetes is an irreversible process due to the quiescent nature of the pancreas during homeostasis. Therefore, exploiting new sources to generate beta cells has become the main therapeutic strategy in regenerative medicine for diabetes.

The three terminally differentiated and fully specialised cell types in the adult pancreas (acinar, ductal and endocrine cells) arise from Pdx1+ embryonic progenitors during development [4]. These cells proliferate and differentiate constantly during pancreatic embryogenesis, with cell fate decisions meticulously regulated by transcription factors such as Neurogenin 3 (Ngn3) (endocrine cells), pancreas transcription factor 1 complex (Ptf1)/Carboxypeptidase A1 (Cpa1) (acinar cells) and Hepatic Nuclear Factor 6 (Hnf6) (ductal cells) (Figure 1b) [4–6]. While adult differentiated pancreatic cells are relatively quiescent in basal homeostasis, certain conditions activate a regenerative program based on expansion of existing cells. Pregnancy triggers proliferation of beta cells, and inflammation and oncogenic stress induce acinar cell proliferation [7–9].

This traditional view of the pancreas in which terminally differentiated cells can give rise only to cells of the same type has been challenged as a result of multiple experimental advances, particularly in single cell RNA-seq analysis [10••,11•], the use of more robust and specific lineage tracing models [4], improved detection methods and a greater variety of stress stimuli [12]. These latest findings have revealed that different cell types in the pancreas are heterogeneous, and they harbour different plasticity potential. Furthermore, the extent of plasticity for each specific cell type mostly depends on the trigger used. This is best exemplified by acinar cells, which if challenged with inflammation or oncogenic stress will

Figure 1



Pancreas scheme. **(a)** *Schematic overview of the pancreatic compartments, consisting of exocrine and endocrine parts.* The acinar and ductal cells compose the exocrine pancreas; the acinar cells secrete digestive enzymes that are channeled to the small intestine via the pancreatic ductal tree. The endocrine cells, confined to the islets of Langerhans, secrete glucose-regulating hormones into the bloodstream. **(b)** *Development of the three terminally differentiated cell types found in the adult pancreas*. Endocrine, ductal and acinar cells arise from the Pdx1+ embryonic progenitors during development. Transcription factors such as Ngn3 (endocrine cells), Ptf1/Cpa1 (acinar cells) and Hnf6 (ductal cells) are key in coordinating cell fate decisions during embryogeneis.

proliferate and transdifferentiate to ductal-like progenitors, but which will adopt a functional beta cell fate if depletion of existing beta cells is combined with transient cytokine administration [13,14].

Here, we will focus on recently uncovered regenerative processes that are involved in phenotypic plasticity of pancreatic cells both *in vivo* and *in vitro*, with special emphasis on plasticity towards a beta cell fate.

In vivo pancreas plasticity

Intra-islet plasticity

Pregnancy was one of the first stimuli described to affect beta cell numbers, and it is thought to induce equal expansion of the beta cell population [7]. Recent data have demonstrated a clear heterogeneity within beta cells, distinguished by Flattop (Fltp1) expression, which partly drives their plastic behaviour (Figure 2a). Tracing experiments using Fltp1-venus reporter transgenic mouse demonstrated that Fltp1 subdivides endocrine cells into two populations and distinguishes proliferation-competent from mature beta cells [15••]. In addition to proliferation, dedifferentiation of beta cells to immature Ngn3-expressing beta cells happens under glucotoxic conditions and this process is reverted when glucose levels are restored [16]. This is consistent with the recent notion derived from single cell RNA-seq analysis of different subtypes of beta cells coexisting in the islets [10••,11•]. Different RNA-seq subtypes could represent cells with different plasticity potentials, an idea that should be formally tested in the near future.

Intercellular conversions within the islets are observed when severe diabetes is induced in rodents (Figure 2a). Complete ablation of beta cells combined with exogenously maintained normoglycemia in mice results in alpha cells transdifferentiating to beta cells without proliferation [17]. This effect is observed from puberty through to adulthood. The generated alpha-derived beta cells are fully functional. However, alpha cells are unable to recover the complete loss of beta cells before puberty, but delta cells are competent to transdifferentiate to beta cells [18]. This data suggests the existence of different temporal windows permissive to alpha and delta cell plasticity. Intriguingly, efficient beta cell regeneration has been observed in children with type-1 diabetes (T1D) or after pancreatectomy [19], but whether the regenerative mechanism involves alpha or delta to beta cell conversion still remains unexplored.

Alpha to beta cell conversion has also been genetically triggered by overexpression of the alpha cell fate repressor factor Pax4 in glucagon cells [20] (Figure 2a). A combination of different lineage tracing experiments showed that upon Pax4-induced alpha to beta cell conversion, a pool of duct lining progenitors is mobilised, proliferate and further replenish the alpha cells which were converted to beta cells. Interestingly, this mechanism is mimicked by chemically inhibiting the Pax4 repressor Arx using gamma-aminobutyric acid (GABA) or Artemisinin treatment [21••,22•]. The molecular characterization of the duct lining progenitors mobilised after GABA treatment could be of special interest to shed light on potential facultative progenitors in the pancreas. In