Development of the endocrine pancreas

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**SUMMARY**
This short review presents the recent breakthroughs in our understanding of the important steps controlling pancreas morphogenesis and differentiation, and on the transcription factors regulating pancreas organogenesis and islet cell differentiation and involved in the specification of the beta and alpha cell lineages. All these studies should permit a comprehensive view of the full genetic program necessary to produce mature and functional beta cells and thus, should be instrumental to guide future strategies for cell replacement therapies in type 1 diabetes.

**Key-words:** Development • Endocrine pancreas • Transcription factors • Research • Review.

**RéSUMÉ**
Développement du pancréas endocrine
Cette brève revue présente les développements récents qui nous permettent de mieux comprendre la morphogenèse et la différenciation pancréatique, et les facteurs de transcription impliqués dans la détermination des lignées cellulaires alpha et bêta pancréatiques. L’ensemble de ces données devrait permettre une meilleure identification du programme génétique nécessaire à la production de cellules bêta pancréatiques matures et fonctionnelles, et ainsi guider les futures stratégies de recherche pour les thérapies cellulaires dans le diabète de type 1.

**Mots-clés :** Développement • Pancréas endocrine • Facteurs de transcription • Recherche • Revue générale.
Understanding the mechanisms controlling multipotent stem cells differentiation into specialized cells during the embryonic life is not only one of the current challenges in stem cell biology but will also have a crucial impact on future cell replacement therapies designed to treat diseases such as type 1 diabetes. Indeed, *de novo* generation of beta cells from pancreatic stem/progenitors occurs essentially during embryogenesis. Understanding the underlying molecular mechanisms is thus essential if we want to recapitulate the beta cell differentiation program and generate functional insulin-secreting cells for therapy starting from plastic cells such as embryonic or somatic stem cells.

In the last years, major breakthroughs in our understanding of the important steps controlling pancreas morphogenesis and differentiation have been obtained [review in 1, 2]. In rodents, the first signs of pancreas organogenesis are the formation of two pancreatic buds (ventral and dorsal) emanating from the foregut endoderm at mid-gestation at the level of the future duodenum. Pancreatic endocrine, exocrine and ductal cells have an endodermal origin. The specification and growth of the two pancreatic buds is controlled by different signals originating from the adjacent mesodermal tissues. Dorsally the pancreatic bud is sequentially exposed to signals from the notochord, dorsal aorta and pancreatic mesenchyme. Ventrally both the cardiac mesoderm and vitellin veins control pancreas development. The two buds later fuse and the pancreatic epithelium branches within the surrounding mesenchyme. Comcomitantly the different pancreatic cell types differentiate from immature pancreatic progenitor cells. The future endocrine cells delaminate from the epithelium, migrate and aggregate in clusters called islets of Langerhans.

Through the analysis of genetically modified mice, a hierarchy of transcription factors regulating pancreas organogenesis and islet cell differentiation was established recently [review in 3, 4]. Two transcription factors, the genes Pdx1 and Ptf1a/p48 regulate the very early steps of pancreatic endoderm specification. Research performed in our laboratory focuses on the transcriptional program implemented subsequently in these early pancreatic progenitor cells to determine their endocrine fate as well as endocrine subtype specification. In this line we identified a master gene, the bHLH (basic helix-loop-helix) transcription factor Neurogenin3 (Ngn3) as a specific marker of islet progenitor cells in the mouse and essential regulator of the endocrine lineage determination [5]. Insulin-glucagon-somatostatin-PP- and the recently discovered Gherelin-producing cells all derive from Ngn3-expressing immature cells [6, 7]. We showed that Ngn3-deficient mice die from diabetes because islet cells are lacking demonstrating that Ngn3 is required for the development of the five pancreatic endocrine cell types including insulin-producing beta cells. These results together with gain of function studies [8, 9] demonstrated that, during development, Ngn3 acts as a genetic switch controlling endocrine fate decisions in multipotential pancreatic progenitor cells. The transcription factors Pax4 and Arx have been shown to be important, downstream of Ngn3, for the specification of the beta and alpha cell lineages respectively [10, 11]. To further understand the molecular and biological characteristics of islet progenitor cells we have generated mice where this cell population can be purified [12]. To find additional regulators of islet sub-type specification and endocrine differentiation we have performed a series of DNA microarray hybridization and determined the complete transcriptome of the purified islet progenitor cells as well as identified the panel of Ngn3-target genes (unpublished). These studies led to the identification of the zinc finger transcription factor IA1/Insm1 a direct target of Ngn3, essential for the maturation of islet cells [13, 14]. Additional known and unknown genes enriched in islet progenitor cells induced by Ngn3 an dil in Ngn3-deficient mice are currently being characterized.

Taken together, these and other studies should generate a comprehensive view of the full genetic program necessary to produce mature and functional beta cells and should thus be instrumental to guide future strategies for cell replacement therapies in type 1 diabetes.

References


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