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Pancreas phylogeny and ontogeny in relation to a 'pancreatic stem cell'

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Abstract

Blood glucose regulation has likely evolved during early vertebrate evolution to allow and secure the concurrent evolution of complex brains and nervous systems: an inner milieu of constant blood glucose levels through millions of years has provided an extra degree of freedom for the brain to evolve without having to *think* of getting energy supply. Key regulators of blood glucose, insulin, and glucagon are produced by the dominating cell types of the pancreatic islet of Langerhans: the insulin producing beta cells and the glucagon producing alpha cells. Interestingly, it appears that the beta cell pioneered the formation or the foundation of the pancreatic organ according to current phylogenetic insights. Such phylogenetic aspects of a pancreatic stem cell are at the end discussed in relation to directed differentiation of embryonic stem cells/ES cells towards therapeutic beta cells. ***To cite this article: O.D. Madsen, C. R. Biologies 330 (2007).***

Keywords: Pancreas; Evolution; Beta cell; Pdx-1; Ptf1A/p48; Nkx6.1; ES cells

1. Introduction: beta cells and diabetes

The pancreatic islet beta cell is uniquely specified to produce and administer insulin to the blood circulation in response to glucose levels. The islet beta cell thus continuously monitors glucose levels, and a glucose increase following food intake is quickly counteracted by increased insulin release – and consequently insulin-induced glucose uptake in peripheral tissues. Functional beta-cell deficiency (and thereby insulin deficiency) is the hallmark of diabetes (T1 vs. T2 diabetes are characterized by a complete vs. relative deficiency of a functional beta cell mass). Insulin deficiency causes hyperglycaemia and diabetes. Long-term elevations of blood glucose lead to damaging glycosylation reactions, eventually causing devastating diabetes late complications. During fasting, glucose levels are maintained via glucagon action where low glucose stimulates glucagon release from the pancreatic islet alpha cell, which in turn stimulates glucose production by the liver. Brain function cannot be sustained during acute hypoglycaemia and unregulated excess insulin release from, e.g., even a small benign insulinoma may cause lethal hyperinsulinaemia-induced hypoglycaemia.

The islet of Langerhans has thus evolved as minute and dispersed organs within the pancreatic tissue possessing a highly specialized ability to sense glucose levels and to secrete insulin or glucagon in adequate

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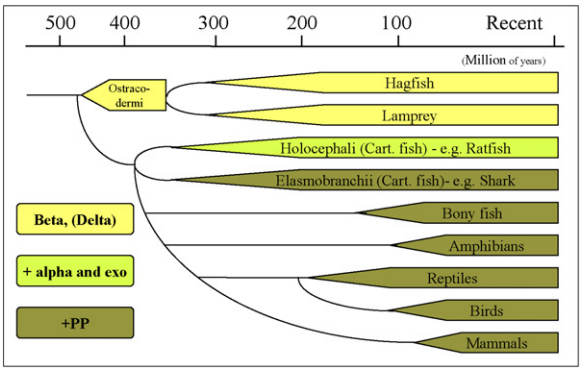

Fig. 1. Phylogenetic relationships between vertebrates are shown in different colours[1] (or grey levels) to indicate the successive entrance of current pancreatic cell types. Figure adapted from [5].

amounts, in order to minimize fluctuations in blood glucose levels. The beta cells have evolved a superior competence to mass-produce and administer insulin – a hormone that is required to sustain life (T1 diabetes patients die if not treated with insulin) – and a hormone that can be an instant killer if overdosed, causing acute and severe hypoglycaemia. Beta-cell-specific suicidal mechanisms allowing regulation/elimination of an excess beta-cell mass are likely reflecting the price to be paid for the acquired competence to administer the potentially deadly hormone, insulin (see [1] for a review).

2. The beta cell as the phylogenetic founder of pancreas

Interestingly, work pioneered by Falkmer and others indicate that pancreas phylogeny was founded by the insulin-producing beta cell (see Fig. 1). In the hagfish and lampreys (our most primitive vertebrate species of today), the first sign of 'a new organ' is found as collections of endocrine cells around the area of the bile duct connection with the duodenum. These endocrine organs are composed of 99% beta cells and 1% somatostatin-producing delta cells. Compared to the more primitive protochordates (e.g., amphioxus), this represents a stage where all previously scattered insulin-producing cells of the intestinal tissue have now quantitatively migrated to found a new organ involved in sensing blood glucose rather than gut glucose. Only later in evolution, the beta cells are joined by exocrine tissue and alpha cells (exemplified by the rat-, rabbit- and elephant-fishes). Finally, from sharks and onwards in evolution, we have the islet PP-cell entering to complete the pancreas [2,3]. Hagfish and lampreys may have one or more endocrine buds – and later the vertebrate pancreas develop as independent ventral and dorsal buds that eventually fuse to become one organ. In the bony fish, a giant islet – known as the 'Brockman-body' is derived of dorsal origin, while the ventral buds give rise to acinar cells, ducts, and smaller islets [4,5].

3. Pdx-1 and other key transcription factors in pancreas formation

Interestingly, amphioxus (proto-chordate) Pdx-1 expression is already narrowed to a confined region of the gut [6]. The presence of Pdx-1 may have been instrumental for the subsequent evolutionary accumulation of beta cells in this region – as well as for the elaborate involvement of Pdx-1 as a beta-cell-specific transcriptional regulator of glucose-responsive genes. Lack of Pdx-1 in vertebrates cause pancreas agenesis [7–9]. Pdx-1 [7,8] and Nkx6.1 [10] are both transcription factors with a restricted expression within the mature pancreatic beta cell. In fact, the co-expression of those two markers in adult islets specifically identifies the beta-cell subpopulation [11]. During pancreas ontogeny, Pdx-1 is expressed within the early budding tissue as well as in the duodenum and antral stomach (albeit at lower levels). Again the co-expression of Pdx-1 and Nkx6.1 selectively specifies all of the early pancreatic progenitors found in the buds of ventral and dorsal origin [11,12]. Such progenitors need to activate *Ngn3* gene transcription to produce the bHLH-transcription factor required for the initiation of the endocrine-cell maturation program [13] – a process regulated by Notch signalling [14].

Ptf1A/p48 is an exocrine bHLH-type transcription factor involved in pancreatic enzyme gene regulation [15] and is also influenced by Notch signalling [16,17]. P48 expression is highly confined within the endoderm to the pancreatic epithelium. It was therefore not unexpected that acinar cells failed to develop in p48 null-mutant mice [18]. Endocrine cells were reported still to form, and eventually localize within the spleen (the spleen forms during condensation of the dorsal pancreatic mesenchyme) [18]. However, later lineage-tracing studies showed that most endocrine cells actually derive from p48-expressing progenitor cells – but also confirmed that some endocrine cells still form in the absence of p48 [19]. Interestingly, Pdx-1 expression from *Ptf1a/p48 cis*-regulatory sequences restores pancreas tissue to *Pdx-1*-null mice [19]. This indicates that p48 and Pdx-1 together are required in the specification of the pancreatic progenitor cell.

[1] Electronic version only.