Chapter 7
Pancreatic Progenitor Cells in Injury and Regeneration

Solomon Afelik and Jan Jensen

1 Introduction

The pancreas is presently receiving attention for different reasons. Pancreatic cancer is among the most lethal cancers, and treatment options are limited. Treatment modalities for acute or chronic pancreatitis are similarly narrow. Furthermore, as the organ is the home turf for the endocrine islets of Langerhans, it is also a keen subject for researchers investigating issues related to the etiology, and possible cures, of type I and II diabetes. It is now known that both the exocrine and endocrine pancreas share a common progenitor. This progenitor may be the culprit in pancreatic cancer development, and at the same time represent the cell type providing most hope to successfully developing an islet cell replacement therapy for diabetes. No wonder then, “pancreatic progenitor existence” as a subject is receiving attention. This chapter provides a review of current issues on the nature and function of both embryonic, and adult pancreatic progenitor cells, finding that research in pancreatic cancer, embryonic development, and adult regeneration starts to build a picture of adult cell plasticity that one day might be harnessed for therapeutic use.

2 Do Adult Pancreatic Stem Cells Exist?

The adult pancreas consists of endocrine and exocrine compartments, which are involved in the regulation of blood glucose levels and intestinal food digestion, respectively. The endocrine pancreas is made up of different hormone producing cells organized into islets of Langerhans, which are closely associated with blood vessels. The exocrine pancreas consists of digestive zymogen-producing acinar cells connected to a network of duct cells that serve as conduits through which the contents of the acini are channeled into the gastrointestinal tract. Although structurally and functionally distinct, both exocrine and endocrine cells of the mature pancreas differentiate from a common pool of pancreatic progenitors that are specified in the posterior foregut endoderm during early embryogenesis. Much is known from mouse pancreatic development, and it is generally
recognized that common gene regulatory networks exist between mouse and human, although differences must exist in the growth and development between these species given the difference in overall size and gestational duration. In the mouse, it is known that the common pancreatic progenitor is determined by the expression of Pdx1/Ipf1 and Ptf1a genes (1, 2). Several other gene regulatory factors are also expressed in this progenitor cell type, many of which are shared among endodermal regions (3–5). A series of intercellular signals between the prepancreatic endoderm and a number of neighboring embryonic tissues are involved in the specification of the pancreatic endoderm. Importantly, under the influence of mesenchymal signals, the early pancreatic progenitor cells undergo a phase of proliferation, characterized by active Notch signaling, prior to differentiation. Notch signaling is often involved in maintaining progenitor populations both during embryogenesis, as well as during adult stem cell maintenance in adult, such as in the neurogenic zones of the brain, the intestinal crypt of Lieberkühn, and the dermal stem cells of the skin as a few examples. The segregation of endocrine and exocrine precursors from the common progenitor pool (6, 7) is also under the influence of Notch signaling and this mechanism is perhaps the best-described aspect of Notch function in the pancreas (8, 9). In the course of embryogenesis and fetal development, the early pancreatic progenitor cells undergo differentiation, resulting in a mature pancreas with fully differentiated pancreatic cells, whereas the early progenitor cells seem to disappear, i.e., cells coexpressing Pdx1, Ptf1a, and active Notch signaling can not be detected in the adult homeostatic organ. Consequently, although embryonic pancreatic progenitor cells are well defined, their presence in the mature pancreas is a subject of controversy. While adult stem cells residing in defined progenitor niches have been well characterized in the skin (basal cells), intestinal epithelium (crypt cells), bone marrow (the marrow can be viewed as the “niche” of the blood), and brain (subventricular zone), there is no concrete evidence of such a spatial niche in the adult pancreas. Alternatively, in multiple differentiated tissues, maintenance and regeneration may be accomplished by resident “adult stem cells,” which do not reside in a spatially defined niche. These are described as undifferentiated cells that have an unlimited ability for self-renewal and give rise to progenitor cells that differentiate into multiple lineages (10–12). Definition and proof of such cells is not straightforward, and often based on a method known as “BrdU labeling retention” (13, 14).

For a group of cells to be unequivocally established as adult stem cells of the pancreas, it is expected that such cells would have a less differentiated phenotype, capable of self-renewal and generate cells that can replenish multiple cell lineages of the pancreas. In an ideal situation, a visualization of the spatial location of such cells relative to differentiated cells with the aid of appropriate molecular markers can be done. To date no cells have been identified in the mature pancreas that fit these criteria; lineage tracing data to track such a defined population has not been possible given lack of a defined marker to initiate the labeling required. A BrdU retention study was described by Duviellie et al. indicating the presence of slow-cycling label-retaining cells located within and around pancreatic islets.