DCAMKL-1: a new horizon for pancreatic progenitor identification

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TYPE 1 DIABETES RESULTS FROM the autoimmune destruction of insulin-producing pancreatic β-cells. Although islet transplantation has shown great potential in the treatment of hyperglycemia in type 1 diabetes patients, availability of donor islets remains a major obstacle (4). Cell replacement strategies aimed at generating functional insulin-producing cells through differentiation of adult pancreatic stem cells/progenitors have been hindered by a lack of suitable markers for their identification.

Pancreatic progenitor cells are important in the regeneration of β-cells and in the development of pancreatic cancer. β-Cell mass undergoes compensatory changes throughout life, particularly during times of increased demand and during injury. This suggests the presence of stem cells/progenitors or some other mechanism of β-cell renewal in the adult pancreas. The lack of demonstrable markers of embryonic β-cell progenitors in the adult pancreas coupled with results from genetic lineage tracing studies showing that β-cells were largely generated by self-replication of preexisting β-cells in adult mice both under physiological conditions and following pancreatic injury (2, 6) cast doubt on the existence of stem cells/progenitors in the pancreas after birth (1). However, several recent studies have demonstrated not only the existence of progenitors in the ductal epithelium for both endocrine and exocrine lineage cells in the adult mouse pancreas (5), but also that some of the new β-cells seen following pancreatic injury in mice arise from progenitors expressing the basic helix-loop-helix transcription factor neurogenin3 (11).

In this issue of American Journal of Physiology, Houchen and colleagues (8) demonstrate the presence of progenitors in the healthy adult mouse pancreas using a novel marker of pancreatic progenitor cells. Using antibodies to the recently discovered putative intestinal stem cell marker DCAMKL-1 (7), they not only show that DCAMKL-1 is expressed in the newborn and adult mouse pancreatic epithelial cells, but that it colocalizes with known pancreatic progenitor cell markers, Ngn3 and nestin. Using DCAMKL-1-based FACS sorting of adult murine pancreatic cells and subsequently transplanting these cells into nude mice, they showed the formation of nodules containing cells expressing the markers of early pancreatic development (Pdx-1), glandular epithelium (cytokeratin 14), and isletlike structures. These results are promising because the transcription factor pancreatic and duodenal homebox gene 1 (Pdx-1) is expressed in embryonic pancreatic progenitor cells and is a key transcription factor in the development of the mammalian pancreas. These progenitors proliferate to enhance the progenitor pool and are maintained in an undifferentiated state through activation of the notch signaling and expression of the transcription factor Sry/HMG box gene 9 (Sox9) (10). Further early β-cell precursors in the pancreas are marked by the expression of the basic helix-loop-helix transcription factor neurogenin3 (3, 9) which colocalized with the expression of DCAMKL-1.

This study thus confirms that multipotent progenitors exist in the adult mouse pancreas. It also provides a tool for isolating these progenitor/stem cells for culturing to generate new pancreas cells. One exciting potential use of these cells could be to generate functional insulin-producing β-cells for use in cell replacement therapies such as in Type 1 diabetes. Future studies will need to be done to differentiate DCAMKL-1-expressing cells into different endocrine cell types. In addition, DCAMKL-1 may be a potential target for anti-stem cell-based therapies in pancreatic cancer.

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REFERENCES
9. Schwitzgebel VM, Scheel DW, Conners JR, Kalamaras J, Lee JE, Anderson DJ, Susel L, Johnson JD, German MS. Expression of
