



Pancreatic Regenerative Medicine and Stem Cells

David Gerber A^{1,2*} Xianwen Yi¹

¹Department of Surgery, University of North Carolina, USA

²Department of Cancer Center, University of North Carolina, USA

INTRODUCTION

Organogenesis of the liver, biliary tree and pancreas is well described in fetal development. Stem/progenitor cells proliferate and subsequently differentiate during early stages of development of the definitive ventral endoderm and these cells contribute to the formation of the foregut. The continued debate persists regarding the reactivation of these processes during the postnatal period. Findings regarding this phenomena are demonstrated for the liver and biliary tree [1, 2], and up to date studies have demonstrated that this process is also occurring within the pancreas [1, 3]. Despite these observations the mechanisms related to the processes involved with postnatal organogenesis are not well understood.

In adult vertebrate tissues, stem/progenitor cell populations of the hepato-pancreatic network persist as a part of a cellular constituency with evidence supporting their contributions to hepatic and pancreatic organogenesis.[4] Recent studies have demonstrated multiple somatic cell niches persisting in specific anatomical locations within the human biliary tree and pancreatic ducts [5]. It's believed that these stem cell populations can play a role in organ repair and recovery from injury. Within the liver and pancreas, division of mature parenchymal cells is related to physiologic turnover and restoration of parenchyma after minor damage. Multiple observations provide supporting evidence that stem/progenitor cells can contribute to organ repair within the setting of chronic injuries [6]. Within the liver these cellular populations are believed to arise in the region near the portal triad and they potentially expand and differentiate across the parenchymal regions.

DESCRIPTION

Developing methods to harness the potential of those organ-specific stem/progenitor cell populations has been the focus of numerous research efforts. Cell transplantation into specific organs was initially approached via classic routes in-

cluding vascular administration. Engraftment efficiencies for cell transplants were low and lots of cells would die during the engraftment process, or worse they might develop into cellular emboli and end up in organs other than the target tissue [7, 8].

Establishing organoids or neo-tissues using pancreatic-derived cellular populations may be a goal of researchers in the field of regenerative medicine. The tissue milieu of the pancreas provides a physiologic environment of blood and oxygen supply that's needed for proliferation and differentiation into functional β cells.(9) A culture environment that's similar to organogenesis provides an environment that supports proliferation of stem cell populations without unwanted differentiation. One approach to establishing organoids/neo-tissues involves creating 3D systems as they more accurately mimic nature's environment by allowing spatial freedom, improved cell to cell interactions, enhanced mixing and exposure to nutrients, and increased area for proliferation. In one approach a 3D micro-gravity culture environment positively affects proliferation and performance of a pancreatic cell population. This 3D environment is useful to a pancreatic progenitor cell population allowing for long-term culture without passage and the ability to differentiate and secrete insulin in response to a glucose challenge [10, 11]. Alternative strategies involve the creation of 3-D bioprinted tissues almost like the work that has been performed in the liver [12].

Success in these endeavors likely requires that the neo-tissue's cellular components mimic the constituent populations, reflecting the epithelial-mesenchymal cell relationships and therefore the cellular foundation of tissues. Cell derived organoids are often seeded with select lineage-stage-appropriate mesenchymal cells as a means of co-transplantation. These partner cells may include angioblasts and their immediate descendants, precursors to endothelia and to stellate cells. Inclusion of those cell types imitates a desirable niche for lineage restriction of stem/progenitors to an islet fate and can

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Corresponding author David Gerber A, Department of Surgery, University of North Carolina, USA, E-mail: david_gerber@med.unc.edu

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facilitate long-term functions in vivo [13]. A completely unique transplantation method, “patch grafting” has been studied as a delivery method that applies cell/grafts to the surface of the pancreas. The patch are often fabricated from a biocompatible and biodegradable material and used as a backing which is coated with a specific extracellular matrix. Research teams have demonstrated successful integration of pancreatic organoids comprised of biliary-tree stem/progenitor cells which engraft and expand within the adult pancreas. Employing a diabetes model these organoids demonstrate increased c-peptide and insulin production with associated blood glucose regulation.

CONCLUSION

The field of pancreatic regeneration is guided by the processes of organogenesis and findings involving repair and regeneration of other tissues. The presence of somatic cell populations that have the potential to differentiate into multiple cellular fates is intriguing and encouraging. Developing an understanding of the mechanisms and pathways related to their innate proliferation and subsequent differentiation will be critical in any efforts to determine how to harness their capacity as a functional therapy.

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