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Pancreatic Regenerative Medicine and Stem Cells

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Abstract

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 ongoing debate persists regarding the reactivation of these processes during the postnatal period. Findings regarding this phenomenon have been demonstrated for the liver and biliary tree, and recent studies have demonstrated that this process is also occurring within the pancreas. Despite these observations the mechanisms associated with the processes involved with postnatal organogenesis are not well understood.

Keywords: Fetal development • Stem/progenitor cells • Postnatal organogenesis

Introduction

In adult vertebrate tissues, stem/progenitor cell populations of the hepato-pancreatic network persist as part of a cellular constituency with evidence supporting their contributions to hepatic and pancreatic organogenesis [1-4]. Recent studies have demonstrated multiple stem cell niches persisting in specific anatomical locations within the human biliary tree and pancreatic ducts [5]. It is believed that these stem cell populations can play a role in organ repair and recovery from injury. In the liver and pancreas, division of mature parenchymal cells is associated with physiologic turnover and restoration of parenchyma after minor damage. Multiple observations provide supporting evidence that stem/progenitor cells can contribute to organ repair in the setting of chronic injuries [6]. In 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.

Literature Review

Developing methods to harness the potential of these 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 including vascular administration. Engraftment efficiencies for cell transplants were low and many cells would die during the engraftment process, or worse they would 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 is 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 is needed for proliferation and differentiation into functional β-cells [9]. A culture environment that is 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 surface area for proliferation. In one approach a 3D microgravity culture environment positively affects proliferation and function of a pancreatic cell population. This 3D environment is beneficial 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 similar to the work that has been performed in the liver [12].

Discussion

Success in these endeavors likely requires that the neo-tissue's cellular components mimic the constituent populations, reflecting the epithelial-mesenchymal cell relationships and the cellular foundation of tissues. Cell derived organoids can be 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 these cell types imitates a desirable niche for lineage restriction of stem/progenitors to an islet fate and can facilitate long-term functions *in vivo* [13]. A novel transplantation method, "patch grafting" has been studied as a delivery method that applies cell/grafts to the surface of the pancreas. The patch can be 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 in the adult pancreas. Using 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 stem cell populations that have the potential to differentiate into multiple cellular fates is intriguing and encouraging. Developing an understanding of the mechanisms and pathways associated with 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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