general anesthesia prior to the skin incision. The polymer tube serving as a scaffold for the cells was composed of a co-polymer of l-lactide and ε-caprolactone (PCL-PLA, 50:50). This co-polymer is degraded by hydrolysis. The matrix is > 80% porous and the diameter of each pore is 100-200 μm. Polyglycolic acid (PGA) woven fabric with a thickness of 0.5 mm was used for reinforcement. Twenty-one TE conduits (TCPC grafts) and fourteen TE patches were used for the repair of congenital heart defects. The patients' ages ranged from 1 to 24 years (median, 5.5 years). All patients underwent a catheterization study and/or computed tomography (CT) scans for evaluation after operation. The patients received anti-coagulation therapy for 3 to 6 months after surgery. **Results:** Mean follow-up after surgery was 424 days (maximum, 38 months). There were no complications such as thrombosis, nor stenosis or obstruction of the tissue-engineered autografts. One late death at 3 months after TCPC was noted in HLHS patients, which was unrelated to the TE graft. There was no evidence of aneurys formation on cineangiography or CT. On examination in late period, all tube grafts were patent, and the diameter of the tube graft increased over time. (110 +/- % of the implanted size)

Conclusions: Biodegradable conduits or pulmonary vessel patches seeded with autologous BMCs showed normal function (good patency up to maximum follow-up of 38 months). As living tissues these vessels may have the potential for growth, repair and remodeling. The TE approach may provide an important alternative to the use of prosthetic materials in the field of pediatric cardiovascular surgery. Longer follow-up is necessary to confirm the feasibility of this approach.

Key Words: Tissue-engineered vascular autografts, bone marrow cells

Clinical Results of Transplantation of Tissue-Engineered Cartilage and Future Direction of Cartilage Repair - Novel Approach with Minimally Invasive Procedure -

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Articular cartilage has very limited potential to spontaneously heal, because it lacks vessels and is isolated from systemic regulation. No treatment has repaired the defects with long-lasting hyaline cartilage. Recently, a regenerative medicine by a tissue-engineering technique for cartilage repair has been given much attention in the orthopaedic field. In 1994, Brittberg et al. introduced a new technology in which chondrocytes expanded in monolayer culture were transplanted into the cartilage defect of the knee. As a second generation of chondrocyte transplantation, we have been performing transplantation of tissue-engineered cartilage made *ex vivo* for the treatment of osteochondral defects of the joints since 1996. This signifies a concept shift from cell transplantation to tissue transplantation made *ex vivo* using tissue-engineering technique. We have reported good clinical results with this surgical treatment. However, extensive basic research is vital to achieve better clinical results with this tissue-engineering technique. I would like to describe our recent research using a minimally invasive tissue-engineering technique to promote cartilage regeneration.

Key Words: Cartilage, tissue-engineering, scaffold

Role of Exocrine Pancreatic Progenitor Cells in Pancreatic Carcinogenesis

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Elucidating the mechanisms that regulates proliferation and differentiation in the pancreas and understanding the mechanisms leading to neoplastic transformation are essential steps for the development of novel diagnostic and therapeutic strategies in the management of pancreatic disorders, such as diabetes mellitus and pancreatic cancer.

The cellular origin of pancreatic carcinoma is one of the most recently studied questions. As a reason for this interest, the pancreas is an organ in which there is little cellular proliferation under normal circumstances, but the little proliferation that does occur is seen in all three components epithelia; ducts, acini and islets. The pancreatic cells, although

essentially quiescent in the normal adult mammal, have a great capacity for proliferation in response to injury, and understanding the events that cause these cells to become independent of normal growth control mechanisms and develop into cancers should have general application to cancers of other organs that are not so readily manipulated.

Most animal pancreatic tumors are characteristically acinar in phenotype and usually well differentiated. This is in striking contrast to the ductal phenotype of most human pancreatic cancer, which may be well differentiated but can also be poorly differentiated or anaplastic. Acinar tumors do occur in humans but are very rare and have a clinical course quite different from those with the ductal phenotype. The origin of human pancreatic cancer from normal ductal epithelium is generally inferred. This implies that carcinogenic events occur in ductal cells. However, the *in vitro* observations provided direct experimental evidence for the transdifferentiation of pancreatic acinar cells or progenitor cells to a ductal phenotype. This initiates strong support for the hypothesis that acinar or progenitor cells may represent the target population for carcinogenic events in the pancreas.

During pancreatic development, the endocrine and exocrine pancreas arise from a discrete locus of prepatterned epithelium in the embryonic foregut. In the mouse, formation of the dorsal and ventral pancreatic buds begins on days E9-10. These buds eventually give rise to a full array of islet, ductal, and acinar elements. A large number of recent investigations using immunohistochemical, cytoablation, RT-PCR, and transgenic techniques have suggested that differentiated pancreatic cell lineages may arise from a common stem cell population within the embryonic pancreatic duct. Targeted deletions of these genes are associated with profound abnormalities involving multiple cell lineages, further suggesting that different pancreatic cell types arise from common precursors within the embryonic pancreatic duct. Investigation of these stem cells has recently been facilitated by the identification of several lineage-restricted transcription factors which are required for normal pancreatic development. These include Pd $\times$ 1, Pa $\times$6, Pa $\times$ 4, Nk $\times$ 6.1, NeuroD, and Ptf1. Among these, the Pd $\times$ 1 homeodomain protein appears to play a critical role in pancreatic stem cell biology, with null mutations resulting in pancreatic agenesis in both mice and humans.

One of the adult models for pancreatic progenitor research, the relative proportion of different pancreatic cell types become dramatically altered in transgenic mice overexpressing TGFα. Following induction of TGFα expression, these mice exhibit progressive pancreatic fibrosis, loss of acinar cell mass, and the development of extensive tubular complexed, termed pseudoductular metaplasia. Based upon the identification of amylase immunoreactivity in individual metaplastic duct cells, as well as the appearance of acini staining positive for mucin, a transition from mature acinar cells to metaplastic duct cells has previously been suggested. Given the relevance of this model to various forms of human pancreatic pathology, including chronic pancreatitis as well as pancreatic cancer, a more precise characterization of participating cell types is required. In this transgenic mice overexpressing TGFα, enhanced cellular proliferation and widespread activation of the Pd $\times$ 1 homeobox gene within TGFα-induced metaplastic ductal epithelium was demonstrated. In addition, this metaplastic epithelium exhibited a pluripotent differentiation capacity, as evidenced by the ability to generate both islet and ductal elements. These findings suggest that metaplastic duct formation in MT-TGFα mice may recapitulate events which normally occur during pancreatic development. These observations may have important implications regarding the cellular lineage responsible for pancreatic ductal metaplasia and neoplasia, and provide further support for the presence of stem cell capabilities within mature pancreatic epithelium.

The most convincing evidence that tumors with a ductal phenotype do not necessarily originate from ductal cells comes from studies of transgenic animals. In transgenic mice, the expression of an elastase promoter-TGFα construct by acinar cells leads to acinar-ductal transformation. Transgenic mice in which c-myc expression is targeted to pancreatic acinar cells develop tumors with a ductal phenotype. These studies points to the phenotypic plasticity of pancreatic acinar cells, although the possible leaky expression of acinar promoters in ductal epithelial cells cannot be excluded at present.

Taken with the recent data from transgenic mice, the possibility of acinar-ductal interconversions suggests a possible role of the pancreatic acinar cell or in the development of pancreatic ductal adenocarcinoma. It may be that there is a population of cells that can easily switch phenotypes and that these represent the progenitor population in the pancreas.

In regards to these facts, we propose that there are clues for both the existence of dormant progenitor or stem cells in the pancreas, exhibiting multipotent characteristics, as well as the possibility that fully differentiated adult exocrine acinar cells retain the capacity to transdifferentiated into ductal-like cells. In this symposium, we raised the question of whether ductal cell regeneration or neogenesis in the pancreas depends on progenitor cells or adult cells that have retained the potential to transdifferentiate. In addition, we suggest the possibility of establishment normal pancreatic exocrine cell line in animals *in vitro*, which may have the potential to be considered pancreatic precursor cells, exhibiting the multipotency of cells undergoing the developmental cascade. This cell line might be useful tools in research determining cellular and molecular mechanisms regulating adult pancreatic differentiation and involving topics with important implications in diseases such as pancreatic cancer and diabetes.

Key Words: Pancreas, ductal adenocarcinoma, cell of origin, stem cell, progenitor cell line