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 under-
standing the events that cause these cells to become indepen-
dent 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 phenoe-
type. 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 focus 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 im-
munohistochemical, cytological, 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 pan-
creatic cell types arise from common precursors within the
embryonic pancreatic duct. Investigation of these stem cell
lines has recently been facilitated by the identification of several
lineage-restricted transcription factors which are required for
normal pancreatic development. These include Pdx1, Pa6,
Pdx4, Nkx6.1, NeuroD, and Ptf1. Among these, the Pd×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
pseudoductal metaplasia. Based upon the identification of
amylase immunoreactivity in individual metaplastic duct cells,
as well as the appearance of actin staining positive for mucin,
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×1 homeobox gene within TGFα-induced metaplastic
duct epithelium was demonstrated. In addition, this meta-
plastic epithelium exhibited a pluripotent differentiation
ability, 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 observa-
tions 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 multi-
potency 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.