Transforming growth factor-alpha (TGF-α) is a polypeptide growth factor that binds and activates the epidermal growth factor (EGF) receptor (1). It belongs to a family of peptides that includes EGF, heparin-binding EGF, amphiregulin, cripto, betacellulin, and viral-derived growth factors such as vaccinia virus growth factor (1, 2). These polypeptides possess six cysteine residues in the same relative position; the resultant disulfide bonds ostensibly lead to similar three-dimensional configurations that are recognized by the EGF receptor. This transmembrane receptor possesses intrinsic tyrosine kinase activity, and is closely related to human EGF receptor-2 (HER-2 or c-erbB-2), HER-3, and HER-4 (3). HER-2 is activated by a family of ligands such as the new differentiation factor (4). The ligands that activate HER-3 and HER-4 have yet to be identified. This complexity underscores the important role of the EGF receptor family in the regulation of cell functions.

TGF-α is found in numerous cell types in normal tissues, implying a physiological role (1). Its overexpression is associated with malignant transformation as evidenced in transfection experiments and by its abundance in many cancers (1, 5). Furthermore, transgenic mice that overexpress TGF-α develop hyperplasia and neoplasia in certain target tissues (6, 7). The pancreas in these transgenes exhibits extensive interstitial fibrosis and pseudoductular metaplasia, which is manifested, in part, by the aberrant presence of amylase and zymogen granules in the duct-like cells (8). This suggests (but does not prove) that these cells may represent redifferentiated acinar cells. Similar histological changes occur in the pancreas of humans with chronic pancreatitis (CP), a disorder that may be caused by chronic alcohol ingestion, pancreatic duct obstruction, and hereditary factors (9). Acinar and ductal cells in the pancreas of humans with CP express high levels of TGF-α and the EGF receptor (10), indicating that the TGF-α transgene is a valid animal model of CP in humans.

In this issue of *The Journal,* Wang et al. (11) have examined the effects of coexpression of human TGF-α and human gastrin in transgenic mice on pancreatic islet mass. They used a previously established TGF-α transgene (7) and a new mouse transgene expressing gastrin in the insulin-secreting beta cell under the transcriptional control of the insulin promoter. Beta cell localization of gastrin was documented by immunostaining. Pancreatic expression was confirmed by Northern blot analysis using a probe specific for the human gastrin gene. Verification that the gastrin precursor can be processed to its bioactive form was accomplished with the use of a radioimmunoassay specific for carboxy amidated precursors. The gastrin transgenes did not exhibit altered pancreatic morphology and their islet cell mass was not increased, indicating that sustained gastrin expression per se does not stimulate islet growth. In the TGF-α transgenes, there was a 10-fold increase in ductal cell mass but no alteration in islet cell mass in comparison with controls. However, some of the metaplastic ductules (6%) in these transgenes exhibited insulin immunoreactivity, indicating that the pseudoductular metaplasia in this model may also recapitulate a protodifferentiated state of the duct cells. Mating the TGF-α and gastrin transgenes produced double transgenic mice expressing TGF-α and gastrin. Remarkably, the pancreas in these double transgenes had a relatively normal histology. There was an attenuated (4-fold rather than 10-fold) increase in ductal cell mass, and a doubling in islet cell mass. These data suggest that islet neogenesis was reactivated in the adult pancreas by high levels of TGF-α and gastrin. This represents a new mechanism of inducing islet neogenesis, which could previously be accomplished by certain manipulations such as partial pancreatectomy or by partial obstruction of the pancreatic duct (11, 12).

The authors suggest that gastrin is promoting the differentiation of insulin-positive cells in the TGF-α-induced metaplastic ducts. They point out that other possibilities include effects of gastrin and TGF-α to stimulate the growth of existing islets or to stimulate new islet formation from stem cells. However, in spite of the increased islet cell mass, the TGF-α/gastrin transgenes did not express increased insulin mRNA levels. Inasmuch as insulin immunostaining and in situ hybridization studies were not carried out in these double transgenes, it is not clear whether insulin is expressed in the pancreatic ductal cells in this model, and what proportion of the islet cells express insulin. Nonetheless, the present findings indicate that the transgene approach is useful for elucidating the factors that regulate and induce islet neogenesis, and suggest that specific growth factors can be identified that stimulate beta cell neogenesis and proliferation. Conceivably, such factors may serve in the future to increase the beta cell mass in diabetic patients (as long as the immune system does not destroy them again in insulin-dependent diabetes), or allow for the in vitro proliferation of islets for subsequent use in transplantation.

Why was the pancreatic histology in the transgenes that expressed both TGF-α and gastrin relatively normal? The pancreatic acinar cell expresses two types of cholecystokinin (CCK) receptors, CCK_A and CCK_B, the latter also being the gastrin receptor (13). While gastrin may act in the transgenes by interfering with TGF-α binding and action, it is possible that it also acts through its receptor to induce normal pancreatic exocrine differentiation and prevent the redifferentiation of the pancreatic acinar cell into duct-like cells. Inasmuch as gastrin expression was beta cell specific, its actions on the exocrine cells supports the concept of an islet-acinar axis whereby islet hormones released into an intrapancreatic portal circulation participate in the regulation of the exocrine pancreas (14). Thus, the double transgene model raises intriguing possibilities regarding strategies for the prevention of CP in humans.

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