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Gumming up the liver: intraductal papillary neoplasm

Recent years have seen widespread recognition that intraductal papillary mucinous tumor (IPMT) of the pancreas is a unique variant of neoplasia derived from ductal epithelium. Likewise, intraductal papillary neoplasia of the liver (IPNL) has been described as a unique variant of cholangiocarcinoma. Unlike the scirrhous and deeply invasive behavior of conventional intrahepatic cholangiocarcinoma, IPNL is a tumor that fills the lumina of the intrahepatic and extrahepatic biliary tree with papillary fronds of mucinous tumor. It is frequently associated with hepatolithiasis; stone formation within the biliary tree. Curiously, IPNL expresses gastric- and intestinal-type mucins, derived from the genes MUC2 and MUC5AC. The mucinous variant of invasive cholangiocarcinoma also expresses MUC2, but not MUC5AC. In this issue, **Ishikawa *et al*** (p. 629) have examined tumor expression of CDX2, a homeodomain protein involved in the regulation of intestinal development and differentiation, and the aberrant mucins MUC2 and MUC5AC. The hypothesis can be advanced that activation of intestinal development, as evidenced by CDX2 expression, plays a role in the development of intraductal neoplasia, much as intestinal metaplasia of the gastric mucosa (in chronic gastritis) and of the esophageal mucosa (in Barrett's esophagus) are considered as risk conditions for cancer. Using immunohistochemistry to examine IPNL, mucinous cholangiocarcinoma, conventional cholangiocarcinoma, IPMT of the pancreas, and conventional ductal adenocarcinoma of the pancreas, the authors find that aberrant nuclear expression of CDX2 is closely related to MUC2 overexpression in mucinous cholangiocarcinoma and in IPNL associated with hepatolithiasis. CDX2 expression also was observed in IPMT of the pancreas. The authors suggest that intestinal differentiation within the biliary tree should be considered as a contributing factor to the development of intrabiliary malignancy. What remains to be determined whether expression of CDX2 itself is of importance, since CDX2 is currently considered to be a tumor suppressor gene, which inhibits cellular proliferation and induces cell differentiation and apoptosis. Regardless, these novel observations extend the general concept that intestinal metaplasia is of critical importance in the development of neoplasia in the tubular portions of the alimentary canal.

Diabetes and the mesangial cell: too sweet

A paracrine relationship exists in the developing kidney between the endothelium and neighboring cells, and there is evidence that such a relationship persists in adulthood. The integrity of endothelial cells, their matrix, and hence capillary structure is maintained in part by production of vascular growth factors by both mesangial cells and podocytes. The mesangial cell is a key player in diabetic nephropathy, as it promotes aberrant matrix deposition in response to high glucose levels. This process is mediated through increased TGFβ1 and angiotensin-2 expression. In this issue, **Singh *et al*** (p. 597) have directly examined the effects of diabetic mesangial cells on endothelial cell growth, matrix formation, and *in vitro* capillary proliferation. After establishing that mesangial cells produce VEGF and angiopoietin -1 and -2, the authors showed that the expression of these vascular growth factors is affected in streptozotocin-treated rats, in which provascular VEGF and angiopoietin-1 decreased and antivascular angiopoietin-2 increased. Interestingly, insulin treatment restored normal levels of the provascular factors, but not of angiopoietin-2, suggesting irreversible damage to the mesangial cells. Similar effects on vascular factor production were obtained with high glucose treatment of naive mesangial cell cultures. Conditioned media obtained from these mesangial cultures was able to significantly reduce endothelial cell growth and *in vitro* capillary formation, and to increase extracellular matrix deposition. This glucose effect also appears to be mediated through decreased production of VEGF and increased production of angiopoietin-2. Owing to the technical challenge presented by the culture of rat glomerular endothelial cells, human umbilical vein endothelial cells were used, and there is ample evidence that these endothelial cells do respond to the vascular factors identified in this study. These results should be ultimately confirmed by direct *in situ* examination of glomerular endothelial cell targeting by soluble factors secreted by mesangial cells in response to high glucose. Nonetheless, these novel findings show that high glucose levels in diabetic patients are not only directly toxic to endothelial cells, but have compounding effects by inducing mesangial cells to produce an antiangiogenic paracrine milieu that results in glomerular lesions. These findings also provide a cautionary note to investigators of

diabetic glomerulopathy, as ambient glucose concentrations may be a critical experimental parameter.

Unexpected nuclear heparanase activity

Degradation of basement membrane and extracellular matrix structures are important features of the metastatic process of malignant tumors. Human heparanase degrades heparan sulfate proteoglycans (HSPGs), which represent the main components of basement membranes and the extracellular matrix. Heparanase expression levels in cancer cells correlate positively to poor prognosis of patients with gastric and breast cancers among many others. The new report by **Schubert *et al*** (p. 535) clearly demonstrated a somewhat unexpected result that heparanase also localized at the nucleus both in cancer and normal cells, suggesting that the enzyme may have another unidentified function. Of interest, recent studies suggested that HSPG-binding mediated nuclear localization of fibroblast growth factors or inhibited DNA topoisomerase I activity. Nuclear heparanase may contribute, as the authors discussed in the manuscript, to the malignant phenotype by modulating transcriptional activity associated with nuclear FGFs or by liberating the inhibitory effect of HSPGs on topoisomerase-I DNA relaxation. Although the exact function played by nuclear heparanase requires further investigation, the present study opens new research avenues in the field.