Volume 81 • Number 2 • February 2001

INSIDE LAB INVEST

NOT "PORIN" OUT THE WATER SPELLS DRYNESS: A novel insight into the pathogenesis of sicca syndromes may come from an abnormal intracellular routing of water channels. The dryness of the mouth observed in patients suffering from Sjögren's syndrome (SS) is usually attributed to the loss of acinar cells in the salivary glands. Two observations suggest that molecules providing transport channels for water across the cell membrane, the aquaporin family, play a role in the pathophysiology of SS, a disease characterized by a marked decrease in the production of saliva. The first observation is that mice with impaired aquaporin function show decreased volumes of salivary excretion. The second is that aquaporins 1 and 5 are known to be expressed in the salivary gland of the rat. Not surprisingly, disturbances in aquaporin-5 can be detected in minor salivary gland biopsies of patients with SS. Using antibodies specifically detecting aquaporin-5, **Steinfeld et al** (Lab Invest 2001, 80:143–148) demonstrate, with elegant simplicity, that patients with SS show an abnormal pattern of immunoreactivity. Whereas in normal controls and patients with dry mouth caused by sarcoidosis most of the reactivity found in the acinar cells is localized in the apical portion of the membrane, in patients with SS the staining is most prominent in the basal portion of the acinar cell. This could explain the decrease in salivary volume. The work of **Steinfeld et al** is the first to indicate that the intracellular routing of aquaporin-5 molecules is abnormal in SS and suggests an alternative explanation for the decrease in saliva production, which is thought to be caused by the immune-mediated destruction of acinar cells. The next challenge will be to figure out how to reroute aquaporin molecules so that the "porin out" of water as saliva can be reconstituted!

ENDOTHELIAL CELLS, HYPOXIA, AND FAS/FASL: Fas (CD95) is a cell surface receptor belonging to the TNF receptor gene family that, upon engagement by Fas ligand (FasL), initiates autocatalytic activation of caspase 8 (also known as FLICE), and through caspase 8 activation, apoptotic cell death of lymphocytes. FasL, a type II membrane protein of the TNF gene family, is expressed on the surface of activated T cells. Activated T cells expressing Fas are killed by other activated T cells expressing FasL. Mice with mutations in either Fas or FasL fail to eliminate activated T lymphocytes and therefore develop (or exacerbate) autoimmunity. It is now well established that both Fas and FasL are also expressed by cells outside of the immune system where these molecules may contribute to elimination of damaged or senescent cells in many other tissues. Human vascular endothelial cells normally express both Fas and FasL but are resistant to Fas-initiated death, possibly because they also express a competitive antagonist of caspase 8, called FLIP (FLICE inhibitory protein). Endothelial cells subjected to oxidative stress (eg, from oxidized low density lipoproteins or hyperoxia) reduce their expression of FLIP, acquire sensitivity to Fas signals, and die. In the current issue of *Laboratory Investigation*, **Mogi and colleagues** (Lab Invest 2001, 80:177–184) have now examined the effects of hypoxia upon endothelial cells. Interestingly, hypoxic human endothelial cells, like hyperoxic cells, also become susceptible to Fas killing (although the authors have not examined whether FLIP is also decreased in this setting). However, despite their sensitivity to Fas signals, hypoxic cells do not normally die. The authors show that this resistance is mediated by proteolytic release of soluble FasL from the hypoxic cells, which acts as a competitive antagonist (or possibly a partial agonist) of killing mediated by membrane-bound FasL. A protective role of soluble FasL has been previously suggested, but this may be the first demonstration in which release of FasL is a regulated response to protect cells from injury. The findings raise the possibility that hypoxic endothelial cells in vivo may, through FasL release, protect other cells in hypoxic tissues from Fas-mediated death. The overall message is that the Fas/FasL system is tightly regulated at several levels and that determination of expression is not adequate to assess the function of these molecules in disease processes.

DCC CONTROL OF CADHERIN: The deleted in colorectal cancer (DCC) gene was first discovered by its frequent loss in advanced colonic tumors and was determined to have a role as a tumor suppressor. From the beginning, however, its function has been a mystery. Structurally, it shares homologies with homotypic adhesion proteins of the neural cell adhesion molecule (NCAM) family, and its loss is often associated with disseminated or

highly metastatic tumors. Yet it is expressed at levels too low on the cell surface to function as a cell-cell adhesion molecule. Subsequent work has clearly established a pivotal role for DCC during embryonic development where it acts to guide axon development via the Netrin response pathway. Netrins are diffusible axon guidance molecules; DCC appears to be part of a receptor pathway that invokes cell or axon migration toward an increasing netrin gradient. So what is the link between DCC in metastatic epithelial cells and embryonic neural development? In this month's *Laboratory Investigation*, **Reyes-Mugica and his colleagues** (Lab Invest 2001, 80:201–210) offer us one answer. Using cultured neuroblastoma cells, they find that when transfected with mutants of DCC (in which the cytoplasmic domain has been removed), the cells assume a bizarre and more rounded phenotype and lose calcium mediated cell-cell adhesion. Surprisingly, it turns out that this effect springs from a dominant suppression of N-cadherin and α- and β-catenin expression. These results are significant because they provide our first evidence of a direct regulatory linkage between cadherin-mediated cell-cell adhesion and the regulation of cell migration by the DCC/Netrin pathway. Moreover, these findings may also resolve the paradox of why DCC appears to function as a tumor suppressor gene. Although not yet examined, if DCC also regulates the activity of cadherin and catenins in epithelial cells, then the role of DCC in modulating tumor spread and metastases will be revealed.

MALIGNANT FIBROUS HISTYOCYTOMA (MFH): FACT OR FANCY? Any classification of tumors, when strictly based on morphological criteria, must be regarded as a collection of arbitrary categories into which we can place tumors to be more easily considered. Soft-tissue malignant fibrous histiocytoma (MFH) was recognized as a morphological entity and became established as a category purely on the basis of a limited spectrum of histopathological appearances. No sooner had this category emerged and risen to become the most prevalent type of sarcoma than its categorical nature was questioned. The wisdom of separating all tumors with an MFH appearance originating in the bone from osteosarcoma was also questioned. Based on clinicopathological studies and immunohistochemistry, many groups engaged in clinicopathological studies of soft-tissue tumors argued that the histological picture of MFH represented the end stage of the progression pathway for many tumor types. Many tumors that had exhibited incontrovertible cell-type characteristics early in their course could be followed to an MFH pattern in later recurrences. In many, if not all, MFH-type tumors, vestigial antigenic activity(ies) suggested the derivation from a specific cell type other than "fibrohistiocytic." **Derré and collaborators** (Lab Invest 2001, 80:211–215) present the results of a comparative genomic hybridization (CGH) study of leiomyosarcomas. Comparing the genetic structural alterations found in leiomyosarcomas to those found in a previous study of MFH, these authors find that leiomyosarcoma and a large proportion of tumors with the MFH pattern share similar CGH profiles. These findings lend support to the notion that MFH represents the final stage of progression likely to be common for many medenchymaltumor types. As the morphological analysis of tissues is complemented and enriched by the simultaneous application of comprehensive technologies (genomics, proteomics), we can expect a vigorous and enlightened remodeling of tumor nosologies.