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INSIDE LAB INVEST

PROTEIN DEGRADATION—REVIEWING THE PROTEOSOME: Proteosomal degradation of ubiquitinated proteins is a final common pathway for many proteins critical in the control of the cell cycle and apoptosis and is now seen as a major pathogenic factor in a wide array of diseases ranging from cancer to neurodegeneration. How proteosomes function is summarized in a timely review by **Naujokat and Hoffman** (Lab Invest 2002, 82: 965–980).

T-CADHERIN LOSS IN CUTANEOUS CANCER: Classical cadherins such as E-cadherin are well recognized calcium-dependent homotypic cell adhesion molecules. Their role in mediating intercellular contact, association with the actin and intermediate filament cytoskeletons, and intracellular signaling via interactions of their cytoplasmic domain with beta and alpha catenin is now well understood. Also understood is the role that the classical cadherins play in tumor invasion and metastasis, with their loss, either by mutation, gene deletion, or transcriptional silencing, marking the acquisition of increased tumor invasiveness and the likelihood of local invasion and distant metastases. Less clear has been the role of the nonclassical cadherins. These molecules share an extracellular domain similar to other cadherins, but have widely dissimilar cytoplasmic domains. Nonclassical cadherins such as CNR-cadherin and 7TM-cadherin do not bind to any of the catenins, but may have other activities such as binding to FYN, a src-family tyrosine kinase. T-cadherin, also know as CDH13 or H-cadherin, lacks a cytoplasmic domain altogether. This protein binds to membranes via a glycosyl phosphatidyl inositol (GPI) lipid anchor. T-cadherin, along with other nonclassical cadherins, sorts to detergent insoluble glycolipid-rich microdomains on the cell surface. Such lipid rafts are specialized cell membrane domains rich in signaling molecules. The presence of T-cadherin in such rafts implicates this cadherin in signal transduction pathways distinct from those of the other cadherins. In tissues such as breast, lung, ovary, and bladder, loss of T-cadherin has been associated with the malignant phenotype, although a causal relationship has not been established. In this issue (Lab Invest 2002, 82: 1023–1029), **Takeuchi and his colleagues** report that loss of T-cadherin expression characterizes invasive, but not necessarily in-situ, squamous cell lesions of the skin. This may occur either by a loss of heterozygosity for T-cadherin on chromosome 1, or by transcriptional silencing by promoter methylation. Whereas the basal layers of all normal samples, and over half of the atypical keratinocytes in cases of actinic keratosis and Bowen's disease, retain T-cadherin expression, only 6 of 56 cases of invasive squamous cell carcinoma did, and even this expression was patchy and focal. Aberrant promoter methylation accounted for a significant fraction of this loss, as confirmed both by analysis of the paraffin embedded samples and by demonstration in cultured A431 cells that the suppression of T-cadherin expression could be reversed by treatment with demethylating agents. Collectively, these findings extend our understanding of the role of this unique cadherin in tumor biology and indicate two pathways by which it may become inactivated in cutaneous lesions. The authors speculate that, given the strong correlation of T-cadherin loss with invasiveness, such loss may be functionally linked to this process, as it is for the classical cadherins. If so, then these results (and others in the literature) point to a more multifaceted role for the cadherin superfamily in regulating cell and tissue organization than previously suspected.

DYSTROGLYCAN—A "NOVEL" MODULATOR OF HEPATIC FIBROSIS: Dystroglycan, a transmembrane protein first described in muscle, is comprised of two subunits encoded by one mRNA that is post-translationally processed to encode for the extracellular α subunit and the transmembrane β subunit. Its α subunit is thought to mediate interactions between extracellular matrix proteins containing laminin-type domains, whereas its β subunit mediates interactions with intracellular dystrophin and related proteins, forming a link between the extracellular matrix and the cytoskeleton. Dystroglycan has subsequently been identified in several cell types and is thought to play a role in basement membrane formation by altering laminin assembly on cell surfaces. The finding of dystroglycan expression in the liver raises the possibility that dystroglycan may function as an important

modulator of basement membrane dynamics during hepatic development, injury, and repair. In this issue (Lab Invest 2002, 82: 1053–1061), **Bedossa et al** determined that dystroglycan is expressed in normal livers and is increased in fibrotic human and rat livers. Cell isolation and characterization studies revealed that hepatic stellate cells were the cells responsible for dystroglycan synthesis and that cell surface dystroglycan was found to mediate stellate cell adhesion to laminin. In light of recent findings illustrating a role for dystroglycan in the formation of basement membranes by facilitating the polymerization of laminins, the authors suggest that its increased expression on stellate cells may facilitate the formation of organized basement membranes lining hepatic sinusoids. This change in extracellular matrix composition and organization lining the sinusoids could, in turn, alter sinusoidal endothelial cell behavior leading to the "continuous capillarization" of the normally discontinuous capillary sinusoids. Such a profound change in vascular structure would then have dramatic effects on the vascular physiology and metabolism of the liver. Thus, this report adds yet another important adhesion/signaling molecule to the already complex list of molecules (integrins, cell surface proteoglycans, etc.) that are involved in mediating bidirectional signaling between the extracellular matrix and the hepatic stellate cell.

BIOLOGY OF HEALING IN REAL TIME: Our understanding of many pathological processes at the organismal level has typically emerged from a series of collated still frames, frozen and captured in time. Rarely can we enjoy a real-time, undisturbed observation of a reaction to injury, and exploit it to obtain unique insights into the mechanisms of defense. Inside this issue (Lab Invest 2002, 82: 1063–1071), **Vollmar et al** take advantage of in vivo microscopy to probe the role of p53 in wound healing. Cell proliferation and apoptosis play an important role in wound healing and are regulated by a distinct temporal pattern. Early in wound healing apoptosis is diminished, whereas during the late stages when scar is being formed, an elevated apoptotic rate reduces cellularity. To probe the role of p53 in this process, Vollmar and collaborators use a compound isolated by Komarov et al (Science 1999; 285: 1733) capable of reversibly blocking p53-dependent transcriptional activation and apoptosis. This molecule, PFTα, protects mice from lethal genotoxic stress caused by anticancer therapy, without promoting the formation of tumors. Using intravital microscopy, Vollmar et al demonstrate that in vivo inhibition of p53 by PFTα accelerates early epithelialization of cutaneous wounds without disturbing wound maturation. This study thus suggests the intriguing possibility that transient inhibition of p53 may be a fruitful therapeutic strategy in cases of delayed wound healing.