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INSIDE LAB INVEST

NUCLEAR ALPHA CATENIN: Pathologists recognize tumors at the cellular level as much by their pleomorphism and loss of tissue architecture, as by any marker of their proliferative capacity. A central mechanism controlling epithelial morphology and epithelial sheet formation is the homotypic calcium-mediated cell-cell adhesion system based on cadherin and its associated cytosolic adapter proteins alpha, beta, and gamma catenin. Beta (or gamma) catenin binds directly to the cytoplasmic domain of classical cadherins such as E-cadherin. Alpha catenin links this complex to the cortical cytoskeleton by binding both beta (or gamma) catenin and F-actin, vinculin, or spectrin. These interactions are subject to inside-out signaling (such as by the phosphorylation of beta catenin) and outside-in signaling (by the clustering and engagement of the cadherins or other adhesion molecules such as those of the IgG superfamily or some of the integrins). Because the loss of function of cadherin or any of the catenins is associated with loss of the epithelial phenotype and portends increased tumor aggressiveness and invasiveness, a tumor suppressor role has long been attributed to these genes and their protein products.

However, the action of these proteins is not limited to their role at the plasma membrane. Beginning with the discovery that beta catenin is also a nuclear protein and a potent transcriptional regulator that controls cell growth via interactions with the *adenomatous polyposis coli* (APC) gene and the Wnt-1 signaling pathway, it has become clear that proteins previously thought to play only structural or organizational roles at the plasma membrane may in fact behave as a type of second-messenger, shuttling between the membrane and nucleus. With the exception of beta catenin and a few other signal receptors that liberate active peptides after proteolysis (such as Notch), the message that these Walter Mitty proteins carry to the nucleus is unknown. However, there is a small but growing list of such proteins, such as the tight junction associated protein ZO1, the cortical cytoskeletal actin binding protein spectrin, and the large polyfunctional adapter protein ankyrin, among others. To this list, **El-Bahrawy and colleagues** now add alpha catenin, as reported in this issue (Lab Invest 2002, 82: 1167–1174).

Using confocal immunofluorescent microscopy and very well characterized antibodies, El-Bahrawy et al demonstrate unequivocally that under some conditions, and in some tumor lines, alpha catenin is present in a speckled pattern in the nucleus. Extending this work to a series of colorectal adenomas and adenocarcinomas, they find a similar localization in a small subset of the carcinomas. The series is too small to know if this observation has any clinical significance, but this is an obvious next question. Importantly, the nuclear localization of alpha catenin does not simply track with beta catenin, making it unlikely that it is simply a passenger as beta catenin moves into the nucleus. Yet, it seems likely (and there is data to support this) that alpha catenin can suppress the transcriptional activity of beta catenin. These observations suggest the possibility of a here-to-fore unknown regulatory circuit that involves alpha catenin and that acts to modify the transcriptional activity of beta catenin, issues that for the present remain largely unexplored. The present study nevertheless opens an interesting new avenue of investigation, and offers us an observation that promises to be important to our understanding of both normal and tumor biology.

METABOLIC DEATH IN CEREBRAL MALARIA: Cerebral malaria can be a dire consequence of infection by plasmodium parasites. Histopathologically, the cerebral microvessels become occluded with intravascular plugs of parasitized erythrocytes, platelets, and macrophages. This local event causes cerebral edema and may be accompanied by systemic changes including hypothermia, dysregulation of glucose levels, coma, and eventually death. Many of the details of these processes have been studied in C57Bl/6 mice infected with *Plasmodium berghei*. In this model, tumor necrosis factor (TNF) is implicated in the pathogenesis of cerebral malaria, possibly through its capacity to induce ICAM-1 expression on cerebral microvascular endothelial cells, which serve as a receptor for binding parasitized erythrocytes. Why do infected mice die? The conventional answer is that death results from brain injury, which causes the systemic sequelae. In this issue, **Piguet and colleagues** (Lab Invest 2002, 82: 1155–1166) challenge this notion. The proinflammatory effects of TNF on endothelial cells are mediated through TNF receptor 1 (TNFR-1), although TNFR-2 may potentiate this response. Plasmodium-infected knockout mice lacking either TNFR-1 or TNFR-2 do show, as expected, partial reductions in cerebral microvessel plugging

and brain edema. Surprisingly, there are no measurable differences between TNFR-1 -/- or TNFR-2 -/- mice in these parameters. Remarkably, TNFR-1 -/- mice still develop hypothermia, hyperglycemia, coma, and death at rates similar to wild type mice, whereas TNFR-2 -/- mice are protected from these outcomes. These data argue that the metabolic disturbances are separable from brain injury and are instead mediated by an endocrine action(s) of TNF involving TNFR-2 but not TNFR-1. In support of the conclusion that TNFR-2 is responsible for the observed metabolic disturbances of infection, the authors show that uninfected TNFR-2 -/- mice are more insulin resistant than either wild type of TNFR-1 -/- mice, but plasmodium-infected TNFR-2 -/- mice are much more sensitive to insulin actions than either wild type or TNFR-1 -/- animals, dying from hypoglycemia following insulin administration. The next challenge is to identify the target tissues and processes that mediate this TNFR-2–dependent response. These data also suggest that TNF may be a physiological regulator of insulin responsiveness and thus may play a role in type II diabetes.

ROVING FIBROCYTES—A DYNAMIC "FIRST RESPONSE TEAM" FOLLOWING INJURY: A population of blood-borne cells, called fibrocytes, capable of differentiating into fibroblasts have been postulated to exist for decades and were isolated and described a decade ago (Bucala R, Spiegel LA, Chesney J, Hogan M, and Cerami A (1994). Circulating fibrocytes define a new leukocyte subpopulation that mediates tissue repair. Mol Med 1:71–81). Fibrocytes are thought to be stem cells derived from bone marrow, making up a small percentage of the circulating cell population (0.5%), but constituting significant numbers of infiltrating cells in wounding models. These cells are known producers of extracellular matrix components (collagen types I & III) and growth factors (including PDGF-A, TGFβ1, MIP1 α and β, and IL1). They express α-smooth muscle actin and, in addition to producing extracellular matrix components, are also thought to contribute to wound contracture. Thus, circulating fibrocytes that have "homed" to a wound site are thought to be significant contributors to the healing/repair response. In this issue, **Yang et al** describe an increased efficiency of differentiation of fibrocytes derived from adherent cells cultured from the peripheral blood mononuclear cell populations of burn victims compared with control subjects (Lab Invest 2002, 82: 1183–1192). This data suggests that either greater numbers of circulating fibrocytes are gated out of the marrow compartments following thermal injury or the circulating fibrocytes of burn victims adhere and differentiate more efficiently than their counterparts in control subjects. The finding of increased serum levels of TGF-β1 in burn victims is consistent with the notion of more efficient differentiation as addition of neutralizing anti-TGF-β1 antibodies suppressed fibrocytes differentiation. The homing of a dynamic circulating fibrocyte population to sites of thermal injury and participating in the healing/repair response suggests that this cell population may be playing significant roles in subsequent scar formation and contractures at the injury sites. Future studies addressing factors controlling gating from the marrow compartments, homing to sites of injury, and differential responsiveness and sensitivities of these cells to local and systemic "wound hormones" may lead to the development of specific interventions that will allow for optimal healing with minimal scaring and contractures, two untoward sequelae of the body's healing response to thermal injury.

THE DOUBLE-EDGED EFFECT OF GASTRIN ON GLIOMA PROGRESSION: The hallmark of malignancy is the capacity of tumors to invade and metastasize. In solid epithelial tumors the invasive program is switched on at a point in progression preceded by carcinoma in situ and may be triggered in response to a combination of signals generated by the tumor cells, stromal cells, or a combination of both. Malignancies of the central nervous system (CNS) represent a somewhat special case for students of tumor pathophysiology. The pattern spread of tumors arising in the central nervous system is different than that of most tumors arising in solid organs. Tumors with a very bland cytological appearance can infiltrate the brain and disseminate at considerable distances. This behavior makes surgical intervention palliative at best. The most malignant tumors of the CNS, those that grow fast and are composed of cells exhibiting marked pleomorphism, very rarely metastasize outside the central nervous system. Distant spread, when it occurs, is almost certainly facilitated by intervention. Inside this issue, **Lefranc et al** begin to address which factors modulate the locally invasive phenotype of tumors derived from glial cells (Lab Invest 2002, 82: 1241–1252). Their work shows that gastrin, a brain neuropeptide, influences astrocytic tumor cell migration by decreasing motility and invasiveness of glial cells in an in vitro assay. The effect is dependent upon the presence of a specific receptor and is partly mediated through a decrease in expression of

RhoA small GTPase. In vitro preincubation of tumor cells with gastrin slows the growth of cells stereotactically implanted in the rat's brain, indicating that the effect is biologically significant. Lefranc et al go on to show that, at least in some instances, gastrin not only influences the motility of tumor cells of glial origin but is also capable of exerting an immunomodulatory effect on the immune system of the recipient animal. Thus, it seems that gastrin can slow the progression of glial neoplasms by a double mechanism acting on independent facets of tumor progression.