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INSIDE LAB INVEST

VEGF-MEDIATED NUCLEAR TRANSLOCATION OF VEGFRs AND β-CATENIN—A PATHWAY FOR TRANSFORMATION?: Vasculogenesis and angiogenesis have been studied intensively over the past several years and significant advances have been made in our understanding of this important process. Interestingly, despite their high incidence in the neonatal and infant age groups, our knowledge of underlying mechanisms involved in the development of endothelial neoplasms is modest by comparison. Although investigators have demonstrated an up-regulation of vascular endothelial growth factor (VEGF) in selected human vascular tumors and when injected into mice, endothelial cells expressing VEGF121 were found to develop into angiosarcomas, underlying mechanisms are still largely undefined. In this issue, **Ilan et al** examine the associations between endogenous VEGF expression, tyrosine phosphorylation and nuclear translocation of VEGF receptors, the phosphorylation and nuclear localization of β-catenin, and the proliferative behavior of hemangioma-derived and primary endothelial cells (Lab Invest 2003, 83: 1105–1115). The studies detailed in this report support the concept that increased endogenous expression of VEGF results in continuous activation of the VEGF receptors, which in turn phosphorylate a variety of cytoskeletal components (including β-catenin) that are associated with a disruption of cell-cell junctions and nuclear translocation of VEGFR2 and β-catenin. The resultant nuclear translocation of β-catenin likely results in interaction with LEF/Tcf transcription factors eliciting up-regulation of cell cycle proteins (CD1) associated with cellular proliferation. These data, coupled with previous data, are consistent with the notion that VEGF levels determine, in part, specific cellular phenotypes (increased proliferative rates in the case of hemangioma-derived EOMA cells) via VEGFR-mediated changes in expression and phosphorylation of selected proteins including β-catenin.

PROTEIN KINASE C CONTROLS CANCER CELL INVASION: It is axiomatic that for a cancer cell to invade and metastasize, it must move. An important aspect of understanding the molecular cell biology of metastasis is thus to understand the mechanisms that control cellular movement. Traditionally, studies of cell movement are complicated by the lack of universal definitions of cell movement and by the arcane methods generally required to measure movement. In this issue, **Laudanna and colleagues** approach this problem by using time-lapse video microscopy and digital image analysis to follow the kinetics of movement of pancreatic cancer cell subclones (Lab Invest 2003, 83: 1155–1163). They also develop a kinetic parameter that combines inputs from the change in membrane area of a cell, the rate of its plasma membrane remodeling, and its rate of directed movement, into a single time-normalized value that they call the mobility score (MS). By examining the MS of a variety of tumor subclones, they find that these lines segregate into two sets: those with high mobility (more invasive), and those with low mobility (less invasive). Moreover, using inhibitory cell-permeant peptides that block the interaction of protein kinase C with its substrates, they demonstrate that the rare zeta isoform of the ser-thr kinase PKC seems to control this process. Further evidence supporting this premise comes from the intracellular distribution of PKC zeta, which is membrane-associated in the high MS cells, and cytosolic in the low MS cells. Collectively, these data point to a novel and important role for this PKC isoform in the control of mobility and presumably tumor invasiveness and suggest that it may also be a novel and accessible target for therapeutic intervention.

PATHOLOGY OF INHALATION ANTHRAX IN CYNOMOLGUS MONKEYS: Anthrax is caused by *Bacillus anthracis*, a gram-positive, aerobic or facultative anaerobic rod-shaped, spore-forming bacterium. Anthrax is considered a significant biowarfare and bioterrorism threat because of its high lethality, especially by its inhalation route. After the recent bioterrorism events involving anthrax in the United States, there is heightened interest in the immunology of this infection and in the production of new vaccines. The low availability of the rhesus macaque, which is a well-characterized model for human inhalation anthrax, prompted **Vasconcelos et al** to study the pathology of inhalation anthrax in the cynomolgus macaque (*Macaca fascicularis*). In their work, the median lethal dose (LD_{50}) and the gross and microscopic pathology of anthrax infection is described in 14 cynomolgus

monkeys after aerosol exposure to spores of the Ames strain of the anthrax bacillus (Lab Invest 2003, 83: 1201–1209). The most common gross lesions were mild splenomegaly, lymphadenopathy, and hemorrhage, particularly involving the meninges and the lungs. Overall, the gross and microscopic pathology of inhalation anthrax in the cynomolgus monkey was remarkably similar to that reported in rhesus monkeys and in humans. This first description of an alternative primate model for anthrax infection may prove valuable for the evaluation of new therapies and countermeasures directed against inhalation anthrax.

HOW MUCH DOES DIVERSITY MATTER?: Life without diversity would not only be boring but would lack the raw material for evolution. Tumor progression, a process that can be envisioned as micro-evolutionary in nature, requires diversity. We have known for a long time that not all tumor cells are equal. Both phenotypic and genotypic heterogeneity are known to occur in neoplasms, but little is known about the degree of diversity present in tumor cell populations. Inside this issue, **Nerlich and coworkers** present data indicating that in squamous cell carcinoma of the larynx, mutations in the TGFBR-II are restricted to small tumor-cell groups (Lab Invest 2003, 83: 1241–1251). The study uses microdissected tumor cells thus eliminating the contribution of nontumoral cells to the pool of DNA analyzed. The exclusion of nontumoral cells may explain why the prevalence of mutations in the TGFBR-II is higher than previously appreciated. But perhaps the most intriguing finding is that different mutations can be identified in different cell groups that are part of the same tumor. The authors speculate that the groups of cells that harbor the mutations may enjoy a selective growth advantage that may well contribute to the clinically aggressive growth of the tumors. The next step will be to clearly show that the genetic abnormalities demonstrated by **Nerlich et al** indeed have the anticipated functional consequences. As we develop therapies targeting specific molecular abnormalities, the degree of tumor cell heterogeneity will become more relevant and perhaps central to the intelligent use of multi-modality molecular therapies.