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In This Issue

The Effectiveness of Chemotherapy in Advanced Breast Cancer

Recent studies in prostate cancer have shown that osteoblasts and osteoblast-derived growth factors, such as IGF-1 and TGF-β-1, have the ability to reverse the adriamycin-induced apoptosis of metastatic prostate cancer cells. These observations were corroborated by the finding that the inhibition of type 1 IGF receptor activity with tyrosine kinase inhibitors led to a reduction in breast cancer tumor growth. The knowledge that breast cancer patients, whose metastases test positive for the estrogen receptor (ER+) have a more favorable prognosis with chemotherapy than estrogen receptor-negative (ER-) patients, led Koutsilieris et al. to hypothesize that, in breast cancer, osteoblasts and/or osteoblast-derived growth factors may differentially affect these metastases' susceptibility to chemotherapy. On pages 86–97, the authors report the results of their studies carried out in ER+ and ER- tumor cell lines. Consistent with clinical observations, the authors find that ER- tumor cells are protected from adriamycin-induced apoptosis in the presence of osteoblasts, osteoblast-conditioned media, IGF-1, and TGF-β-1, while ER+ cells gained no such protection. They go on to suggest that the cytotoxicity of chemotherapy is favorably enhanced by bone-derived mediators in ER+ breast cancer.

Correlating HIV-Associated Dementia with Molecular Markers

HIV-associated dementia (HAD) is a neurological condition that appears in 15 to 20% of AIDS patients, with an annual incidence of 5 to 10% in patients with AIDS. The associated cortical neuronal and synaptic loss appears to be mediated through an indirect mechanism, as infections of astrocytes and neurons are infrequently observed. The majority of earlier studies indicate that HAD may be related to several markers, including unintegrated viral DNA and multinucleated giant cells, and that HAD severity may correlate with the number of HIV-1 infected macrophages and cerebrospinal fluid RNA viral burden. Recently, Adamson et al. reported that the levels of the viral protein gp41correlated with the severity of HAD. On pages 98–109, they report that increased levels of gp41 also correlate with the rate of progression of HAD, and that this correlation was also observed for iNOS and HAM56, a marker of microglial/macrophage activation. Based on these observations and those of previous studies, the authors suggest that the increase in gp41 may be a result of decreased protein degradation, allowing for signalling that leads to the induction of TNF-α, IL-1-β, and iNOS. They further speculate that the inhibition of these signalling pathways has potential therapeutic benefits.

Hypooxygenation and Creatine Kinase Activity in Congenital Heart Disease

The enzyme creatine kinase (CK) catalyzes the transfer of phosphate groups between creatine and ATP. This helps the cell maintain an optimal ATP:ADP ratio. Through the use of isozymes that localize to the mitochondria and the cytoplasm, the cell is able to efficiently transfer energy from the mitochondria to the cytoplasm for consumption. In the cytoplasm, CK is found as a dimer, either as a homodimer of the brain isozyme (CKBB) or the muscle isozyme (CKMM), or as a heterodimer (CKMB) that is unique to the cardiac muscle. Studies in several models of cardiac hypertrophy, ischemia and failure, including left ventricular hypertrophy and coronary artery disease, have described increased levels of CKMB and variable CK activity. These observations led Kessler-Icekson et al. to examine the levels of expression of the CKMB isozyme in right ventricular biopsies from patients with con-

genital heart disease, hypothesizing that decreased oxygenation of the blood and tissues of cyanotic patients may mediate a difference in isozyme distributions when compared to non-cyanotic patients. They report on pages 110–116 that no difference was found between the cyanotic and normally oxygenated patients. They suggest that the high levels of CKMB activity that were found in both patient groups may be sufficient to support hypooxygenated myocardium, or that these levels may reflect the highest attainable by the heart, as the literature contains no reports of higher levels. Alternatively, this observation may suggest that the arterial oxygen level is not an independent regulator of CK-isozyme distribution.

Immune Responses in Atherosclerosis

Recent studies have suggested that the development of atherosclerosis is initiated, in part, by the recruitment of activated T-lymphocytes into early atherosclerotic lesions. As in inflammatory sites, it appears that this recruitment is mediated by several adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (ELAM-1, or E-selectin). Furthermore, it has been noted that various stressors, including TNF-α, lipopolysaccharide, and hemodynamic turbulence can induce the co-expression of these adhesion molecules and heat shock protein-60 (Hsp60), explaining the presence of anti-Hsp60 reactive T-cells in the arterial intima. This raises the speculation that a preventive therapy for atherosclerosis could be administration of immunosuppressants. Early results, however, have been contradictory. While aspirin has been shown to lower the incidence of myocardial infarction and stroke in men, CyA-mediated T-cell suppression has actually increased atherosclerosis in mice. Studies of the mechanism of action of aspirin have, to date, focused on its effect on NF-κ-B-regulated transcription. Amberger et al. have now investigated the role of aspirin, CyA, and indomethacin in regulating the expression of ICAM-1, VCAM-1, ELAM-1, the heat shock proteins Hsp60 and Hsp70, and monocyte chemoattractant protein-1 (MCP-1) in endothelial cells. Beginning on page 117, they report finding that aspirin was able to suppress the expression of adhesion molecules on endothelial cells, while CyA and indomethacin are unable to do so. Interestingly, all three induced the expression of Hsp60 and Hsp70. The authors use these observations to suggest that aspirin's suppression of adhesion molecule expression prevents T-cell infiltration during atherogenesis, despite the concurrent upregulation of the heat shock proteins. This would also explain the observed increase of atherosclerotic lesions with CyA administration.

Controlling Transgene Expression

While conventional transgenic systems have greatly enhanced our understanding of gene function within living organisms, they are not without limitations. One of the largest remaining hurdles is the uncontrolled fashion in which the transgene is expressed. This can lead to improper interpretation of results, unexpected phenotypes, or embryonic death. On pages 129–137, Huang et al. report finding a method whereby green fluorescent protein (GFP) transgene expression could be controlled in a time- and level-dependent manner using a tetracycline based system. In this system, transgene expression is controlled by a tetracycline-responsive transcription factor, which can bind the tet-responsive element of a promoter only after a conformational change is induced by doxycycline, a tetracycline analogue. In this report, the authors have been able to express GFP specifically in oligodendrocytes by placing the myelin basic protein promoter upstream of the tetracycline-dependent transcription factor. Furthermore, altering doxycycline doses allowed the control of GFP transgene expression. The authors speculate that such a system could be extremely useful for gene therapy, since the cell-type-specific promoter, coupled with doxycycline dosage, would allow temporal and spatial transgene expression to be tightly controlled.