Volume 83 • Number 10 • October 2003

INSIDE LAB INVEST

T CELL RECEPTOR GENE RECOMBINATION IN ATAXIA TELANGIECTASIA HETEROZYGOTES: Ataxia-telangiectasia (AT) causes progressive cerebellar degeneration. AT is associated with high rates of T cell lymphoma, with translocation breakpoints at T cell receptor gene loci. The disorder is caused by homozygous defects in the *ATM* gene. *ATM* is vital for recognition and repair of double-strand DNA breaks that are generated as a consequence of DNA damage. The gene is also required for handling of double-strand DNA breaks generated during normal recombinational processes, including T cell receptor gene rearrangement in the course of T cell ontogeny. Aberrations in T cell receptor recombination can promote translocations involving TCR genes that may themselves provoke further genetic instability. Recent work from Lantelme, Giachino, and colleagues linked AT to increased frequency of a population of peripheral T lymphocytes with defective TCR expression. These T cells expressed RAG genes (which mediate T cell receptor gene recombination) and may therefore provide ground for further recombination, even in mature T cells. It is possible that this population up-regulates or sustains expression of recombinogenic enzymes because they express defective T cell receptors. Although AT disorder is rare, the frequency of *ATM* heterozygotes is high, at around 1% of the population. ATM heterozygotes have moderately increased risk for breast cancer. In the current issue (Lab Invest 2003, 83:1467–1475), **Lantelme et al** extend their earlier observations on AT to *ATM* heterozygotes. Heterozygotes had elevated numbers of CD4+CD3 low peripheral T cells. In cell lines derived from these T cells, this phenotype was associated with expression of recombinogenic enzymes RAG1, RAG2, and/or terminal transferase. T cell receptor rearrangement intermediates could be detected in two of the lines. This work extends the earlier findings on AT to a much larger collection of individuals. Although the extent to which *ATM* heterozygosity is associated with T cell leukemia and lymphoma is still uncertain, the evidence provided here implies that such a link will be substantiated and include disorders representing more mature T cells. It will also be of great interest to determine whether the expression of recombinases in this context directly promotes other forms of chromosomal instability.

TUMOR PROMOTION BY ERYTHROPOIETIN: Erythropoietin regulates red blood cell production by promoting the survival, proliferation, and differentiation of erythroid progenitors in the bone marrow. Erythropoietin also has entered the therapeutic arena as a treatment for the anemia associated with renal disease, and that which follows cancer chemotherapy. The effect of this hormone is likely more broad, however, and recent studies have provided evidence for its functional role in the survival of endothelial cells and neurons. The cellular receptor for erythropoietin, in turn, has been implicated in embryonal brain development, and erythropoietin signal transduction may promote neuronal survival in response to hypoxia. In this issue, **Batra et al** identify the expression of erythropoietin and its receptor by common pediatric tumors types, such as neuroblastomas and various brain tumors, Ewing's sarcomas, Wilms' tumors, rhabdomyosarcomas, and hepatoblastomas (Lab Invest 2003, 83:1477–1487). Many of these tumors have a neural origin. Cell lines derived from these tumors were found to respond to erythropoietin stimulation by an increase in the expression of anti-apoptotic genes and an increase in the production of different angiogenic growth factors. These findings reveal a biologically significant, erythropoietin-responsive character to certain tumors that may be potentially exploited for therapeutic benefit. This effect may be particularly relevant for those tumors of fetal or embryonic origin. These data also raise the warning that erythropoietin treatment may promote tumorigenesis in certain clinical settings.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND ANTI-ANGIOGENESIS: OLD TREATMENTS, NEW USES: Since its discovery over 100 years ago, aspirin (a cyclooxygenase inhibitor) has been heralded as a wonder drug, being used to alleviate symptoms in a myriad of conditions ranging from headache to thrombosis. Since their discovery, other cyclooxygenase inhibitors have been developed including indomethacin and more recently the COX-2 inhibitors. These nonsteroidal anti-inflammatory drugs (NSAIDs) have been routinely used as effective anti-inflammatory and analgesic drugs in a variety of diseases. The latest generation cyclooxygenase inhibitors, specific cyclooxygenase-2 (COX-2) inhibitors, are currently widely prescribed as anti-arthritic drugs.

Following their introduction as therapeutic agents, it was recently discovered that, in addition to their expected therapeutic effects, NSAIDs can affect the incidence and progression of certain human cancers. Experiments performed using COX-2 deficient mice provided confirmatory evidence as to the potential importance of modulating this enzyme in cancer patients. To date, despite their growing acceptance as effective anti-cancer agents, the underlying mechanism(s) of their actions remain incompletely understood. In this issue, **Yoshida et al** present evidence supporting the concept that COX-2 activity plays a role in tumor-induced angiogenesis (Lab Invest 2003, 83:1385–1394). Using a murine sponge implant model, these investigators have previously demonstrated an increase in VEGF expression following addition of exogenous COX-2 or exogenous prostaglandins and inhibition of this COX-2 induced angiogenesis with administration of antisense oligonucleotides specific for VEGF mRNA. In this report they identify the COX isoforms that mediate angiogenesis and characterize the downstream molecules responsible for this phenomenon. These studies illustrate the importance of the COX-2/VEGF pathway as a dynamic modulator of both tumor-induced and reactive (reparative) angiogenesis, and serve as an illustration of the general nature of this angiogenesis inhibition and the widespread, varied effects such treatments are likely to have on diverse patient populations.

FINE CLASSIFICATION REFINED: The major aim in the classification of diseases is to find the most effective therapy and accurate prognosis. Etiologic classifications have the advantage of being precise, and in many instances an effective therapy is available. The next best alternative providing access to a therapy is the mechanistic classification. Particularly in the era of molecular medicine we begin to have the means for molecular intervention that corrects the pathogenetic factor(s) directly causing dysfunction and morphologic lesions. As one shifts from classifications based on ultimate (etiology) and proximal causes (mechanism), the therapeutic value diminishes, although the prognostic impact may remain. Phenomic or morphologic classifications can be augmented by a number of means that interrogate cells or tissues at the molecular genomic level. In this issue, **Baumgartner et al** report on subtypes of enteropathic T cell lymphoma (ETL) that are defined by chromosomal alterations and by the presence or absence of micro-satellite instability (Lab Invest 2003, 83:1509–1516); interestingly, the spectrum of genetic alterations detected exhibited a pattern-dependent morphology. The study shows that monomorphic ETL emerges as a very distinct type and suggests interesting candidate loci that could be involved in the progression of these aggressive tumors.