Volume 83 • Number 3 • March 2003

INSIDE LAB INVEST

COX-2 RESPONSE IN THE LUNG—REGULATION VIA p38: Pulmonary complications of sepsis and other inflammatory lung diseases often times have disastrous consequences for patients suffering from these conditions. Mitogen-activated protein kinases (MAPK) have been implicated in the signaling pathways at play in the pulmonary responses to these conditions. In this issue, **Ermert et al** demonstrate a role for p38 in a Cox-2/thromboxane synthase axis in bronchial and vascular smooth muscle cells after lipopolysaccharide (LPS) treatment. Specifically, the authors demonstrate that this signaling pathway is responsible for enhanced pulmonary artery pressor responses, edema formation, as well as bronchoconstriction (Lab Invest 2003, 83: 333–347). These results suggest that the p38 signaling pathway is a potential therapeutic target for several inflammatory conditions.

NONHEPATOCYTE CYP39A1 SITE CITED—NEW INSIGHTS FOR SIGHT PLIGHTS?: The alternate route to bile acid production from cholesterol begins with hydroxylation to oxysterol and is followed with 7α-hydroxylation. The latter reaction is catalyzed either by CYP39A1 or CYP7B1 oxysterol 7α-hydroxylases. These enzymes have different substrate preferences, with the former favoring 24-hydroxycholesterol. 24-hydroxycholesterol is produced primarily in the brain, which is also the major reservoir for this species. It had been thought that 24-hydroxycholesterol mobilized from the brain is released into the circulation and is delivered to the liver for metabolism by hepatic CYP39A1 oxysterol 7α-hydroxylase. In this issue, **Ikeda and coworkers** show that CYP39A1 oxysterol 7α-hydroxylase is also expressed in the nonpigmented epithelial cells of the eye, which produce the aqueous humor (Lab Invest 2003, 83: 349–355). The focal expression of CYP39A1 in liver and nonpigmented epithelial cells suggests specialized functions in both tissues, which, in the case of nonpigmented epithelial cells, is surely not the production of bile. Instead, the authors offer intriguing speculations about eye-specific functions: the enzyme may serve to prevent entry of 24-hydroxy–cholesterol into the eye chamber. More interestingly, the enzyme may initiate production of a bioactive cholesterol derivative, possibly a steroid hormone, that could be important for homeostatic maintenance of the eye. This work reveals a new metabolic system that could well be important for pathogenesis in the eye, including the development of glaucoma.

THE QUEST FOR THE POWER OF PREDICTION: A statistician who has made major contributions to the field of machine learning said to a collaborator, “Tell me what you want. If you want to predict, I can help you, but if you want to control, only God can help you!” It thus seems that the power of predicting is in reach, and we all agree that shifting from a reactive mode (responding to disease) to a predictive mode (anticipating the probability of disease) is a desirable and laudable goal for medicine. The result of recent progress in many areas of pathology and therapeutics will be a personalized and predictive medicine. How far can we see? When it comes to somatic tissues, and more specifically to the life history of tumors derived from somatic tissues, the work of the “Rotterdam group” (**Hatanpaa et al**; Lab Invest 2003, 83: 419–428) suggests that genetic alterations detectable in prostate cancer can forecast which patients will have a poor outcome. Although the study is a retrospective case-case comparison and has a limited number of patients in each category (progressors versus nonprogressors), the length of follow renders the data set worthy of follow up and validation. Two notions put forth by the Rotterdam team deserve comment. The first, as presented in this issue, is that the predictive feature of progression in prostate cancer seems to be a gain of genetic information in chromosome 8. There is also a suggestion that gain of a second region in 3p may also be informative to predict progression. Thus, it seems that gain of function drives the malignant behavior of prostatic carcinoma. Whether the presumed gain(s) of function need to occur in a certain, perhaps specific, background of losses remains undetermined. The second point, as shown in previously published work, is the indication that the gain of genetic information in the short arm of chromosome 8 is an event that can be detected in microscopic carcinomas. Thus, it is possible to think that the event that determines the natural history of prostate cancer occurs early enough to be of clinical relevance. The cumulative contributions of

these types of studies in *Laboratory Investigation* will not give us divine powers but will certainly improve our ability to predict!

RUNNING ON EMT: Migrations of epithelial cells during embryonic development are accompanied by an epithelial-mesenchymal transition (EMT), in which epithelial cells detach, leave their sites of origin, and become motile. Similarities between this process and early stages of cancer progression have suggested that the same regulatory processes may be involved. Hence, there is great interest in the mechanisms through which epithelial cells can be induced to undergo EMT. **Ackland and coworkers** describe a variant of PMC42 human mammary carcinoma cells, PMC42-LA, that undergoes a growth factor-regulated EMT (Lab Invest 2003, 83: 435–448). In contrast to PMC42 cells, only a small percentage of PMC42-LA cells express the mesenchymal marker vimentin. However, incubation with epidermal growth factor (EGF) switches the culture to 100% vimentin positive within a matter of days. EGF reduces expression of E-cadherin, a critical aspect of EMT, and upregulates components of the extracellular matrix (ECM) associated with EMT. Increased migration was observed on some substrates. The availability of a relatively normal epithelial model for this process should facilitate investigation of several factors relevant to the progression of carcinoma. Does EGF serve an instructive role in these cells, or will activation of generic growth factor-regulated pathways suffice? To what extent does suppression of E-cadherin bypass the EGF requirement? It has been proposed that a subset of early stage breast carcinomas are already associated with poor prognosis and that they can be recognized through transcription profiling of tumors. Do developmentally programmed composite "master phenotypes," that may be activated through a relatively small number of epigenetic or genetic changes, contribute to the genesis of inherently aggressive tumors? Better understanding of these issues may eventually make it possible to either prevent or reverse EMT in carcinogenesis.