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INSIDE LAB INVEST

JUST SAY NO TO ASPIRIN: Aspirin, through its irreversible inhibition of cyclo-oxygenase in platelets, has antithrombotic activities that can improve outcomes in patients who have had recent myocardial infarcts. Since antiplatelet therapy is also of benefit following angioplasty, there is a general sense that aspirin may be useful in a broader spectrum of vascular diseases. Unfortunately, aspirin also inhibits cyclo-oxygenase activity in the gastric mucosa, which is often a limiting toxicity. Nitric oxide (NO) is known to be cytoprotective of gastric mucosa, perhaps by increasing blood flow, and several companies are exploring the idea of reducing the side effects of aspirin (or of other nonsteroidal anti-inflammatory drugs) by coupling them to NO donors. This could have additional benefits in the setting of vascular injury, where NO can be both anti-inflammatory and antithrombotic as well as cytoprotective. In this issue, **Yu and colleagues** (Lab Invest 2002, 82: 825–832) test this idea by comparing aspirin to NO-releasing aspirin for their effects on pathological vascular remodeling and lipid accumulation following femoral artery injury in hypercholesterolemic (ie, apoE-deficient) mice. The data are clear-cut: in this model, NO-aspirin reduces intimal expansion, whereas aspirin does not. The bigger surprise was the mechanism. NO-aspirin prevents arterial intimal growth, at least in part, by inducing apoptosis of intimal cells. The proapoptotic activities of NO in this setting should not be a complete surprise; high levels of NO can damage vascular cells in vitro through actions as a free radical. Nevertheless, the hope of therapeutic apoptosis may just have moved from the cancer ward to the vascular clinic.

IS TYPE 2 DM AN AUTOIMMUNE DISEASE?: Human diabetes mellitus (DM) is divided into type 1 (insulin-dependent), believed to be caused by autoimmune-mediated destruction of pancreatic islet β cells, and type 2, characterized by resistance of peripheral tissues to the actions of insulin and not thought to involve the immune system. Both forms of the disease have significant genetic contributions. Type I DM research has strongly benefited from use of the nonobese diabetic (NOD) mouse strain, which mimics many aspects of the pathogenesis of the human disease, including an association with homologous immune response genes (class II major histocompatibility complex molecules). Type 2 DM is commonly associated with obesity and has been linked to genes related to metabolism, rather than immunity. In two companion papers in this issue **(Haskell et al; Junger et al)**, a new mouse model of type 2 DM is introduced, namely the NZO/H1 strain (Lab Invest 2002, 82: 833–842; 843–853).These animals are, as expected, obese. This strain is related to the NZW and NZB autoimmune mouse strains, long used as a model for human lupus. Moreover, the propensity for developing obesity and type 2 DM can be enhanced by crosses of NZO females with NZB males, just as lupus-like disease is brought out by crossing NZW with NZB animals. The NZO strain seems to have a defect in regulation of B1 B cells, a lymphocyte subset associated with production of protective natural antibodies and of harmful autoantibodies. Perhaps the biggest surprise is that when a targeted mutation of B cell development is introduced into these mice, diabetes, but not obesity, is suppressed. In other words, autoimmunity may play a role in type 2 as well as type 1 DM, at least in the mouse. This new mouse model will provide a valuable tool for future genotypic and phenotypic analyses and may provide new insights into human DM as well.

MOLECULAR MULTI-TASKING; EPO & BREAST CANCER: Erythropoietin (EPO) is the cytokine that regulates erythropoiesis. Its biological effect on red cell precursors is mediated by interaction with a specific transmembrane receptor expressed at the surface of erythroid progenitor cells. The binding of EPO to its receptor enables tyrosine phosphorylation of Jak-2, which in turn mediates mitogenesis and prevents apoptosis. As it is the case with other gene products, the physiological role they play is constantly expanding. It is somewhat surprising that when the gene encoding EPO is disrupted in mice cardiac malformations and anomalies of the vascular network are prominent components of the KO phenotype. Inside this issue, **Arcasoy et al** (Lab Invest 2002, 82: 911–918) report high levels of expression of EPO and its cognate receptor in human breast cancer cells. Although it seems logical to predict that EPO-EPOR expression would be somehow linked to hypoxia, no correlation is

demonstrated by the reported studies. To test the functional role of EPO expression in breast cancer cells, Arcasoy et al use a rat model. Growing EPO expressor cells in chambers implanted in syngeneic rats test the effect of inhibiting EPO synthesis using different strategies. One-time administration of a neutralizing anti-EPO antibody, an excess of soluble EPO receptor or an inhibitor of Jak2 kinase, reduce by 45% the depth of tumor growth in a dose-dependent manner. These results suggest that EPO and EPO-R expression in breast cancer is functionally significant. Whether EPO transcription is regulated by estrogen no doubt will be high on the research agenda, as work from other groups studying EPO expression in the uterus suggests that this is indeed the case for the female reproductive tract. What makes a pathway may be more a matter of context than receptor-ligand interaction.

EGR-1'S ROLE IN STRAIN-INDUCED VASCULAR REMODELING: Remodeling of the microvasculature is an important, dynamic, continuous process modulated by a diverse number of stimuli including oxygen tension, a number of soluble factors, and hemodynamic forces such as mechanical cyclic strain and fluid shear stress. Remodeling has been associated with degradation of extracellular matrix and several studies have demonstrated that inhibition of protease activities blunts or abrogates microvascular remodeling and angiogenesis. In this issue, **Yamaguchi et al** demonstrate the induction of MT1-MMP expression by microvascular endothelial cells in response to cyclic strain (Lab Invest 2002, 82: 949–956). In addition, they also show that the induction of MT1-MMP correlates with the transient induction of the Egr-1 transcription factor, and loss of the Egr-1 binding site on the MT1-MMP promoter abrogates the induction. As nucleotide recognition elements for Egr-1 are present in the promoters of several other genes (including tissue factor, TGF-1, PDGF-A, and uPA) known to be important in vascular responses, it is attractive to suggest that, in concert with these genes, MT1-MMP endows the affected endothelial cells with a proteolytic phenotype that enables timely remodeling of the subendothelial matrix. Since MT1-MMP is a membrane-tethered protease, it is conceivable that MT1-MMP may also function as a sheddase, modifying the cell surfaces of the endothelial cell, possibly modulating responses to a variety of soluble factors as well as adhesive interactions with adjacent cells and underlying matrix. Thus, Egr-1 seems to be a pivotal transcription factor, regulating the expression of a number of endothelial genes in response to a variety of physiologic and pathophysiologic stimuli. However, much is still to be learned regarding its effects and specificities on gene induction when acting in concert with other transcription factors on the promoters of these genes.