In this issue

By John Ashkenas, Science Editor

Action at a distance in the hyperoxic eye

(See article on pages 717–725.)

Exposing newborns to high levels of oxygen, as occurs during the care of premature infants, can have several unfortunate effects on vessel development in the eye, including the loss of vessels within the retina and prolific growth of leaky vessels in the (normally avascular) vitreous body of the eye. This latter effect, which can lead to retinal detachment and blindness, occurs only after the infant is returned to normoxic conditions. Intravitreal neovascularization is puzzling because it occurs at a considerable distance from the retina, where the angiogenic factor VEGF is produced. Based on their experiments with mice deficient in the inducible nitric oxide synthase (*iNOS*) gene, Sennlaub and colleagues suggest a novel mechanism to explain this pattern of growth. In wild-type animals, iNOS is induced shortly after normal oxygen levels are restored, and it appears to block the formation of vessels in the retina by its effects on VEGF receptor function in neighboring cells. In the absence of iNOS, retinal revascularization is improved, preventing the development of hypoxic conditions that drive the aberrant vascular formation in the vitreous body. Blocking iNOS activity with a specific inhibitor has a similar beneficial effect, suggesting an additional target for therapies to block the retinopathy of prematurity.

Arterial wound repair in DDR1 knockout mice

(See article on pages 727–735.)

Following arterial injury from balloon angioplasty, smooth muscle cells (SMCs) proliferate within the vessel wall, narrowing the vessel and often restricting blood flow to a dangerous degree. Within the neointima, these vascular SMCs deposit collagens and other ECM components, which they bind and interact with in various ways. Considerable effort has centered on the adhesive receptors expressed during neointima formation, and Hou et al. show here that a novel collagen receptor, unrelated structurally or functionally to the better-studied integrin family of ECM receptors, plays a key role in this pathological response. The discoidin domain protein DDR1 is a member of a small family of receptor tyrosine kinases that bind collagens in soluble or insoluble form and directly transduce signals across the plasma membrane. Knockout mice lacking this protein are viable and normal in many respects, including the structure of their arteries. However, SMCs from these animals are specifically deficient in their ability to adhere to or migrate on collagen, prompting Hou and colleagues to examine the responses of *DDR1*$^{-/-}$ mice to arterial injury. The authors find that, following angioplasty in the carotid artery, the mutant animals form a dramatically smaller neointima than do wild-type controls, raising the hope that inhibition of DDR1 at the time of treatment could repress this response in humans as well. Hou et al. also speculate that the contribution of SMCs to atherosclerotic lesions could be affected by the loss of DDR1 function, an idea they propose to test by crossing the *DDR1* mutation into an atherosclerosis-prone genetic background.

Molecular mimicry and neurodegenerative disease

(See article on pages 737–744.)

Autoantibodies to neuronal ion channels are implicated in several disorders of the central nervous system, including Rasmussen's encephalitis, in which antibodies cross the blood-brain barrier and bind to glutamate-gated calcium channels (GluRs). Binding of autoantibodies to GluR3 activates the channel and causes the death of specific populations of neurons. Although this condition can be modeled by immunizing animals with the GluR3 protein, it is not clear whether autoimmune responses to GluR3 normally initiate the disease. On the contrary, Koustova and coworkers now report that mice mount a specific immune response to the GluR proteins after being infected with the leukemia virus LP-BM5. Self-specific antibodies accumulate in the neocortex and elsewhere in the brain, and Koustova et al. find that such brain-derived autoantibodies are biologically active, activating calcium channels in cultured cells and blocking interactions between these channels and their normal ligands. These antibodies also kill cultured neurons, both by directing complement-mediated lysis and by excitotoxicity, in which elevated intracellular calcium concentrations lead to cell death. Because the antibody's effects can be blocked by adsorbing away IgGs that bind to the virus itself, it appears that the self-reactivity of the antibody results from molecular mimicry between some viral epitope and the GluR proteins. However, the authors note that preadsorbing the antibody with viral proteins only reduces and does not eliminate the effect of the antibodies on ligand binding to calcium channel, suggesting that epitope spreading after infection with the virus generates other channel-specific autoantibodies that can block channel function and promote neurodegeneration.