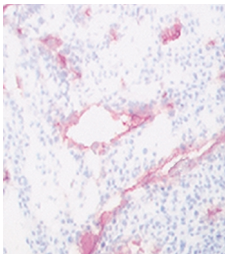
In this issue

By John Ashkenas, Science Editor

Microtumor-induced vascular development

(See article on pages 777–785.)

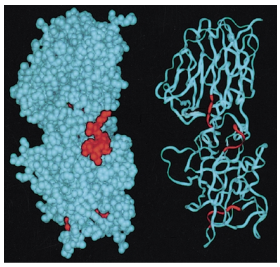
Solid tumors above a critical size become hypoxic at their core. The upregulation of the angiogenic factor VEGF under these conditions is widely thought to explain tumor vascularization and continued proliferation, but Vajkoczy and coworkers point out that some metastatic tumor cells express low levels of bio-active VEGF in a constitutive manner and appear to require VEGF signaling even at a very early stage. These authors used intravital microsopy to show that glioma cells interact with the host vasculature and begin to induce angiogenesis at times well before the tumor mass has reached this limit. Small cell clusters or individual glioma cells, implanted in a vascularized tissue, spread along existing vessels. The resulting tumors did not appear to grow around the existing vessels, as would have been predicted by the so-called "cooptation" model. Rather, infiltrating cells that broke from a tumor mass appeared to migrate along these vessels and induce the sprouting of new ones, which could be distinguished from normal vessels by their disorganized structure and their leakiness. Evidently, at least for this $VEGF^+$ tumor cell type, vascular outgrowth does not begin with hypoxia, but occurs as a continuing process of growth and remodeling, starting early in tumor progression.



Bacterial proteins cause autoimmunity in the antiphospholipid syndrome

(See article on pages 797–804.)

With the availability of complete genome sequences from many microbes, it is now possible to learn, purely through database analysis, which species carry a peptide sequence of interest. Blank and colleagues previously found a six–amino acid antigenic determinant associated with antibodies from people with the autoimmune disorder antiphospholipid syndrome (APS). Since close matches to this short sequence exist in proteins from a variety of common human pathogens, they set out to test the possibility that molecular mimicry between the bacterial proteins and the endogenous host protein explains the loss of self-tolerance in APS patients. Blank et al. treated mice with extracts from several bacteria and a pathogenic yeast, most of which they knew to express such a sequence. Several of the target sequence-expressing bacteria induced high-affinity antibodies specific for the same autoantigens identified in APS patients. For at least two of the bacterial species, these antibodies were clearly pathogenic, in that, when purified, concentrated, and transferred to naive recipient mice, they could cause symptoms of APS, particularly a prothrombotic phenotype and a high rate of spontaneous abortions. Curiously, the mere presence of these antibodies was not sufficient to cause autoimmune disease, since the mice that produced these antibodies showed no such symptoms. Along with their various bacterial preparations, Blank et al. challenged the animals with the tetanus toxoid protein, which contains three sequences that are similar in their 3-dimensional structure to the target peptide. Because this treatment also induced pathogenic autoantibodies, it may be important to test whether this widely administered vaccine confers any risk of APS to humans.



Oxidative damage to eNOS by tissue peroxynitrite

(See article on pages 817–826.)

The peroxynitrite anion ($ONOO^-$) is blamed for chemically modifying a variety of proteins and lipid species under conditions of inflammation and oxidative stress. Building on their present studies of the peroxynitrite's effects on the endothelial NO synthase (eNOS), Zou et al. propose a biochemical pathway by which such damage can be propagated in vascular tissue. eNOS and the other NOS's are more or less directly responsible for the formation of this molecule, since they produce two highly reactive species, NO and the superoxide radical ($O_2^{\cdot-}$), which spontaneously combine to form peroxynitrite. In its ordinary role, eNOS consumes molecular oxygen, coupling this redox reaction to the production of NO from arginine. However, the enzyme can also operate in an "uncoupled" mode, where it does not produce NO but simply releases reactive oxygen species, such as peroxide and superoxide. Even in a purified preparation of recombinant eNOS, the combination of coupled and uncoupled catalysis generates NO and superoxide, and therefore yields peroxynitrite. Crucially, Zou et al. find, eNOS itself is highly susceptible to damage by peroxynitrite, which removes a zinc atom that is complexed to both subunits of the normal eNOS homodimer, leaving an enzyme that operates in the uncoupled mode. The structural change thus favors the production of more superoxide and peroxynitrite, which can damage not just eNOS, but also other susceptible enzymes in the endothelium. Zou et al. show that the peroxynitrite-induced loss of zinc from eNOS — and the consequent shift to uncoupled catalysis — is not simply an in vitro process, but that the same pattern of events occurs in cultured endothelial cells exposed to oxidizing levels of glucose, as well as in the tissues of diabetic mice.