Atherosclerosis Induced by PCSK9 Gene Transfer (p 1684)

Bjørklund et al describe a faster and easier method for inducing atherosclerosis in mice.

Genetically engineered mice lacking the Apoe or Ldlr gene are the go-to models for studying hypercholesterolemia and atherosclerosis. However, numerous rounds of breeding are required to study the effects of other genetic modifications in these strains. Such procedures are not only time consuming and costly, but they involve the use of a large number of animals. Now Bjørklund and colleagues have devised a new method to induce hypercholesterolemia and atherosclerosis in wild-type mice and hamsters by a single injection of a viral vector encoding proprotein convertase subtilisin/kexin type 9 (PCSK9), a protein known to increase levels of LDL, or “bad” cholesterol in humans and mice. When placed on a high-fat diet the injected animals displayed persistent hypercholesterolemia and atherosclerosis. The team then used this technique to examine the effect of diabetes on atherosclerosis. They found that when injected with the PCSK9 vector, diabetic mice developed more severe hypercholesterolemia and atherosclerosis than non-diabetic mice. The speed and simplicity of this new approach should expedite atherosclerosis research not only in mice and hamsters, but other mammals as well.

Sorafenib Cardiotoxicity Increases Mortality (p 1700)

Duran et al discover how the anticancer drug sorafenib causes cardiac injury, and how to protect against its cardiotoxic effects.

Sorafenib is a protein kinase inhibitor that has proven to be an effective treatment for solid tumors such as renal cell carcinoma. However, in clinical trials the use of sorafenib is associated with significant cardiotoxicity. Duran and colleagues have now confirmed the cardiotoxicity of this drug in animals; showing that mice given sorafenib are more likely to die after myocardial infarction. The team reports that treatment with sorafenib induces necrosis in myocytes in vitro and in vivo, while causing pathological hypertrophy in surviving myocytes. Moreover, in both in vitro and in vivo experiments, the drug inhibited stem cell proliferation, which the authors suggest could diminish the healing process and thereby exacerbate cardiac injury. Indeed, they found fewer proliferating cells in infarct border zones of sorafenib-treated mice versus untreated mice. Importantly, treatment with the beta-blocker, metoprolol reduced the cardiotoxic effects of sorafenib. On the basis of these observations the authors suggest that treating cancer patients on sorafenib with metoprolol might be a simple way to protect against heart damage.

Ferroxidase I Activity and Heart Failure (p 1723)

Low ferroxidase activity is a predictor of mortality in heart failure patients, report Cabassi et al.

Heart failure is associated with aberrant production of damaging free radicals derived from both oxygen and nitric oxide. In the body, iron(II) catalyzes the production of these free radicals, while iron(III) is relatively less reactive and less toxic. The enzyme ferroxidase, which is part of the serum protein ceruloplasmin (Cp), converts iron(II) to its safer form iron(III) but, surprisingly, higher levels of Cp have been associated with heart failure, myocardial infarction and mortality. Cabassi and colleagues have now found that while Cp levels were indeed increased in a cohort of 96 elderly heart failure patients, ferroxidase activity was significantly decreased and was lowest in those with most severe symptoms. Ferroxidase was, in fact, a strong predictor of mortality and its activity was inversely related to the level of nitrotyrosine-bound Cp—a modification to the protein known to inhibit its ferroxidase activity. This modification, the team showed, was caused by peroxynitrite—a potent oxidizing and nitrating agent—which is known to be increased in heart failure patients. Altogether the results suggest that low ferroxidase and high nitrotyrosine-bound Cp levels may be good indicators of heart failure prognosis, and that increasing ferroxidase activity might be a worthy aim of future therapies.
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