LXR Controls Macrophage Iron Metabolism (p 1196)

M2 macrophages diffuse potential iron bombs in atherosclerotic plaques, report Bories et al.

During an intraplaque hemorrhage in an unstable atherosclerotic plaque, red blood cells rush in and accumulate. Once inside, they become prone to rapid lysis, resulting in the release of free iron molecules, which can oxidize lipids, induce cell death and ultimately promote atherosclerogenesis. But macrophages present in the plaque help to prevent such disastrous outcomes. Bories and colleagues wanted to identify which macrophages were involved in minimizing the damage. Hence, they compared two key macrophage populations—the M2 and resting macrophages (RM). They found that the M2 macrophages were more adept at ingesting red blood cells than RMs. As a result, M2 macrophages exhibited stronger—in fact almost exclusive—staining for iron content. The team went on to show that the uptake of iron by M2 macrophages induced the transcription factor LXR, which in turn promoted the expression of ferroportin, a protein involved in iron export. The iron released from macrophages by ferroportin is normally bound to a protein called transferrin, which renders the iron incapable of inducing oxidative damage. The authors suggest that boosting the activity of M2 macrophages or LXR could limit the progression of atherosclerotic lesions.

SYNJ2BP Regulates Angiogenesis (p 1206)

Synaptojanin-2 binding protein (SYNJ2BP) is a novel anti-angiogenic factor, report Adam et al.

While angiogenesis is known to be problematic in several diseases, including cancer, it is essential for embryo development and for tissue growth and wound healing in adults. Angiogenesis is regulated by the vascular endothelial growth factor (VEGF), which transforms endothelial cells of an existing vessel into tip cells that can then grow into new stalks. During this process, the protein DLL4 is activated in the tip cells and signals, via Notch, to suppress the expression of VEGF receptors in the cells of the growing stalk. This repression prevents the generation of too many tip cells. Indeed, loss of the DLL4-Notch signal results in the formation of hyper-dense vascular networks. Adam and colleagues looked for proteins with activity in the newer stalk cells. Enhancing this process, the protein DLL4 is activated and, when repressed, caused excessive microvascular density in an in vivo assay. Conversely, over-expression of SYNJ2BP prevented angiogenesis. They found SYNJ2BP. The protein was expressed in vascular endothelial cells and, when repressed, caused excessive microvascular density in an in vivo assay. Conversely, over-expression of SYNJ2BP prevented angiogenesis. The team showed that SYNJ2BP actually stabilizes the DLL4 protein, thus maintaining its Notch-inducing activity in the growing stalk. Enhancing the activity of SYNJ2BP or the DLL4-Notch pathway could therefore be a viable strategy for suppressing angiogenesis.

Nox4 Promotes Autophagy During Energy Stress (p 1253)

Nox4 promotes tissue-saving autophagy during energy stress, say Sciarretta et al.

Autophagy, a catabolic process in which the cell digests its own components, might sound a bit macabre but it is an essential for survival during periods of energy starvation such as myocardial ischemia. By devouring and then digesting dysfunctional proteins and organelles, autophagy provides energy-poor cells with the substrates needed for ATP production, thus limiting the extent of tissue damage. The mechanisms controlling the induction and the progression of autophagy are not fully understood. It is known, however, that energy deprivation promotes the production of reactive oxygen species (ROS) in cells. Thus, Sciarretta and colleagues asked whether Nox4—an enzyme that generates ROS—is induced in energy-deprived cardiomyocytes and, if so, whether it could then regulate autophagy. The team showed that depriving cardiomyocytes of glucose, which is known to stimulate autophagy, led to increases in both Nox4 and ROS. Moreover, autophagy was suppressed and the cells died more readily when Nox4 was absent. In vivo studies revealed that the hearts of mice starved for 48 hours had increased levels of Nox4 and autophagy and that these increases were crucial for maintaining cardiac function. In fact, upon experimental ischemia, Nox4-null mice exhibited larger infarct sizes. Taken together, these results suggest that boosting Nox4 and autophagy in patients experiencing prolonged myocardial ischemia could protect against the loss of cardiac tissue.