Endothelial Activation by Shear Stress (p 410)

Fu et al report how two atherosclerosis risk factors synergistically activate one molecular mechanism in vascular endothelial cells.

Both disturbed blood flow and high cholesterol are known to promote the formation of atherosclerotic plaques in blood vessels. Previous work by this research team had shown that high cholesterol prompts the endothelial cells lining the blood vessels to increase their surface expression of a molecule called ATPSβ. This molecule binds to γδ T cells, which are enriched at early-stage atherosclerotic plaques. The team has now discovered that the surface expression of ATPSβ is increased by disturbed blood flow as well. ATPSβ is found within the cell associated with mitochondria, as well as at the cell surface, but both disturbed blood flow and high cholesterol promoted the molecule’s recruitment to lipid rafts, which translocated it to the membrane. The γδ T cells recruited by increased ATPSβ cell surface expression released inflammatory cytokines. These cytokines caused further activation of the endothelial cells, leading to an increase in the proinflammatory cell adhesion molecule—VCAM-1. Since cell surface ATPSβ expression appears to set off a chain inflammatory reaction, perhaps blocking its translocation might be investigated as a means to slow atherosclerosis.

IPC-Induced Protein SNO Protects Against Oxidation (p 418)

Nitric oxide protects cardiac proteins from permanent oxidative damage by getting in the way, say Kohr et al.

Part of the tissue damage caused by cardiac ischemia is the result of a sudden burst of reactive oxygen species (ROS). Damage can be reduced if the heart experiences a brief ischemic attack before a more serious prolonged one, in a process called preconditioning. It is known that nitric oxide (NO) plays a role in the cardioprotective mechanisms of preconditioning, and one way it is thought to do so is by S-nitrosylation—the addition of nitric oxide (NO) moieties to proteins. The hypothesis is that protein nitrosylation, which is a reversible modification, prevents the more damaging irreversible modification of proteins by oxidation. Nitrosylation can be measured by a technique called SNO-RAC (resin-assisted capture). Here, Kohr et al have modified this method to measure nitrosylation and oxidation simultaneously (SNO-RAC/Ox-RAC). After preconditioning mouse hearts, the team found that the level of S-nitrosylation was increased in 27 proteins. Furthermore, 76% of these proteins showed decreased oxidation after ischemia/reperfusion injury compared with proteins that had not been exposed to preconditioning. Kohr et al, thus, provide one more piece of the preconditioning puzzle that might be exploited for cardioprotective therapies in the future.

GSK-3β Improves Mesenchymal Stem Cell Therapy (p 478)

Cho et al have found a way to boost the heart-fixing benefits of bone marrow-derived stem cells.

Many stem and progenitor cell types have been investigated for their potential to promote tissue regeneration and to repair injured hearts. Although bone marrow-derived mesenchymal stem cells (BM-MSCs) have shown particular promise, there is still room for improvement. BM-MSCs do not differentiate efficiently into cardiomyocytes in vivo and, thus, do not contribute to repair as much as they potentially could. Cho and colleagues recently found that a kinase called GSK-3β, which activates a variety of intracellular proteins and pathways, can increase cardiogenic gene expression in BM-MSCs in vitro. With this in mind, the team looked to see whether pretreating BM-MSCs with GSK-3β would improve their ability to differentiate and, thus, repair heart injury in vivo. It did. In mice that had suffered heart attacks, injection of GSK-3β BM-MSCs improved survival rates compared with injection of control BM-MSCs. Left ventricular function was improved, remodeling was reduced, and capillary density was increased. Improved survival and capillary density were both dependent on the growth factor VEGFα, which was upregulated by GSK-3β. Interestingly, however, ventricular function and reduced remodeling were not. Clearly, there are VEGFα-independent mechanisms of GSK-3β action, but whatever those are, this kinase could provide a much-needed boost to cardiac regenerative therapies.
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