PAD Inhibition and Atherosclerosis (p 947)

Preventing neutrophils from casting nets curbs atherosclerosis development, say Knight et al.

Like Spiderman spinning a web to catch a villain, neutrophils cast chromatin NETs (neutrophil extracellular traps) to capture pathogens. But while this innate immune tactic is useful for defeating foreign infiltrators, it can also damage blood vessels, both by stimulating inflammation and by promoting blood clots. Indeed, these NETs have been found to aggravate the development of atherosclerotic plaques. The formation of NETs by neutrophils is regulated by the enzyme peptidylarginine deiminase. Thus, to determine whether inhibition of this enzyme might attenuate atherosclerotic lesion formation, Knight and colleagues gave atherosclerosis-prone mice a high-fat diet and daily injections of the PAD inhibitor-Cl-amidine. After 11 weeks, the Cl-amidine treated mice produced fewer NETs and had significantly smaller atherosclerotic lesions. The team also confirmed that the effect of Cl-amidine was neutrophil dependent. While neutrophil depletion alone decreased atherosclerosis Cl-amidine treatment offered no further protection suggesting the inhibitor treatment decreased lesion formation by inhibiting NET formation. The specificity of PAD inhibition—eliminating NETs, but not other immune functions—makes this enzyme an appealing target for possible atherosclerosis prevention.

YAP and Cardiovascular Development (p 957)

YAP is a critical regulator of cardiovascular development, report Wang et al.

YAP is a major effector protein of the Hippo pathway, which regulates organ growth and size in animals. Indeed over-expression of YAP in the embryonic mouse heart causes it to become enlarged, while inactivation of YAP leads to cardiac hypoplasia. In the adult mouse, YAP promotes proliferation of vascular smooth muscle cells (VSMCs) following blood vessel injury. Wang and colleagues therefore wondered whether YAP might also promote VSMC proliferation during vasculogenesis. To test this, they genetically engineered mouse embryos lacking YAP in both cardiomyocytes and VSMCs and observed thinning of the right and left ventricle walls, as well as thinning of the walls of the carotid and thoracic arteries, both of which were associated with reduced cell proliferation. They also found that VSMCs isolated from the engineered mice proliferated less in culture and had increased expression of cell cycle arrest genes. In one of those genes, Gpr132, the team found a binding site for TEAD—a protein that interacts with YAP to silence genes—and increased recruitment of histone deacetylase—a chromatin modifier involved in gene silencing—in the absence of YAP. Given YAP’s role in cardiovascular development, further studies on this protein could provide new understanding of mechanisms underlying congenital cardiovascular disorders.

St3Gal4-Deficiency and Atherosclerosis (p 976)

Döring et al discover that inhibiting sialyltransferase activity in myeloid cells reduces atherosclerosis.

The recruitment of white blood cells to the endothelium is a first step in atherosclerotic plaque development. Deciphering how leukocytes are recruited and how it could be stopped are therefore key goals of atherosclerosis research. It is known that chemokine receptors on the surface of the leukocytes interact with ligands on the vessel wall endothelium, causing the leukocytes to stick and roll along the wall, finally coming to a stop. It is also known that the addition of a sialic acid moiety—sialylation—to one particular leukocyte chemokine receptor is required for interaction with its endothelial ligands. However, whether sialylation is a requirement for other receptor-ligand interactions is not known. Döring and colleagues found that mouse myeloid cells that lacked the sialyltransferase enzyme St3Gal4 had impaired interactions between chemokine Ccl5 and its receptors, while interactions between Ccl2 and its receptor were unaffected. Importantly, the deficiency in Ccl5 interaction was enough to reduce atherosclerotic plaque development in atherosclerosis-prone mice. Blocking sialyltransferase activity in leukocytes may therefore be an effective therapeutic strategy for slowing or stopping atherosclerotic lesion progression, suggest the authors.