FXR in Vascular Calcification (p 1807)

It might seem unlikely, but boosting the activity of a bile acid receptor prevents vascular calcification, report Miyazaki-Anzai et al.

Besides being highly expressed in liver, kidney, and intestine where bile acids are abundant, the bile acid receptor FXR has also been reported to be expressed in vascular smooth muscle and endothelial cells and has been found in atherosclerotic lesions. What it is doing in blood vessel walls, however, was a mystery. Miyazaki-Anzai and colleagues discovered that FXR was highly induced in both a cellular and mouse model of aortic calcification. Boosting FXR activity using the FXR agonist drug INT-747 inhibited calcification in vascular cells, whereas blocking FXR did the opposite. Importantly, oral delivery of INT-747 prevented vascular calcification in a mouse model of chronic kidney disease. Clinical studies have shown that more than half of patients with chronic kidney disease die of cardiovascular complications, with one common cause being calcific arterial disease. Thus, perhaps INT-747 (currently in clinical trials for diabetes and primary biliary cirrhosis) could also be used to reduce the risk of death in chronic kidney disease patients.

Proepicardial Organ Specification in Zebrafish (p 1818)

Liu et al have identified two factors that prompt the formation of cells that form other cells that form the heart.

The factors BMP4 and Tbx5a, the team say, prompt formation of the zebrafish proepicardium (PE)—a cluster of cells that develops into the epicardium, which in turn gives rise to essential cell types and structures of the heart. BMP signaling had been previously implicated in PE development from studies in chick embryos, but which particular BMP member might be responsible was unknown. The team looked at the timing of expression of different BMPs in zebrafish embryos, and BMP4 fitted the bill. Furthermore, BMP4 mutants lacked expression of PE developmental markers. By contrast, Tbx5 had been reported in chick embryos to be important for migration of PE cells. The team was thus surprised to find that in zebrafish, Tbx5 was essential early in PE development, earlier than BMP signals, in fact. Knock out of Tbx5 did not affect BMP4 expression, however, suggesting that the two act independently. Because epicardium activation in the adult zebrafish is essential for heart regeneration, the newly identified factors might suggest a means to regenerate injured human hearts, too.

ABCA1, ABCG1, and Efferocyte Apoptosis (p 1861)

Yvan-Charvet et al have discovered how two cholesterol-clearing proteins protect macrophages from apoptotic cell death.

In atherosclerotic vessels, clearing away dead cells keeps the lesions from quickly getting worse. The dead cell trash collectors are the macrophages, but theirs is a risky business, for the very act of cleaning up endangers their lives. Or so it would were it not for the cholesterol transporter proteins ABCA1 and ABCG1. It has been shown that mice that lack these transporters have an excessive accumulation of dead macrophages throughout their tissues and atherosclerotic lesions. Yvan-Charvet et al have now shown that when macrophages lacking the transporters gobbled up cellular corpses, the ingested membrane lipids and cholesterol triggered the assembly of NADPH oxidase complexes. This resulted in an excessive intracellular burst of damaging reactive oxygen species, which in turn prompted the activation of apoptotic pathways. The transporter proteins, which are normally upregulated in macrophages after apoptotic cell ingestion, appear to keep a cap on reactive oxygen species production—no doubt by ridding the macrophage of its enormous lipid load.
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