

DRP1 Regulates Cardiovascular Calcification (p 220)

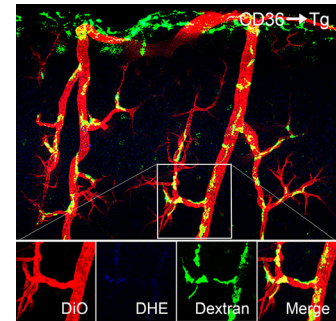
Mitochondrial regulator DRP1 promotes vascular calcification, report Rogers et al.

Blood vessel calcification is associated with adverse hemodynamics and cardiovascular conditions. Once believed to be a passive process of aging, it is now known that calcification involves the active differentiation of smooth muscle cells (SMCs) and valve interstitial cells (VICs) into bone-like cells (osteoblasts). Many of the biological processes related to vessel calcification—such as cell differentiation, apoptosis, and calcium homeostasis—involve mitochondrial dynamics, and it has been shown that mutations to the mitochondrial regulator dynamin-related protein 1 (DRP1) are associated with calcification of heart tissue in mice. Rogers and colleagues have examined the potential link between DRP1 and calcification in humans. They found that in human carotid artery plaques and in calcified valve tissue—from patients undergoing aortic valve replacements—DRP1 staining was elevated in regions of calcium deposition. Furthermore, DRP1 levels were also high in cultures of human SMCs and VICs undergoing osteoblast differentiation, and inhibition of DRP1 attenuated both SMC and VIC calcification. The findings suggest that human DRP1 promotes vascular calcification and that this condition may be prevented or attenuated by therapeutic inhibition of DRP1.

CD8 α^+ Dendritic Cells, IL-10, and Atherosclerosis (p 234)

Haddad et al identify the necrosis sensor DNGR1 as a potential therapeutic target in atherosclerosis.

The accumulation of apoptotic cells and necrotic debris within atherosclerotic plaques is associated with both chronic inflammation and an increased risk of plaque rupture. But how the insufficient clearance of dead cells leads to inflammation in atherosclerosis is not well understood. Haddad and colleagues hypothesized that the dendritic cell NK lectin group receptor-1 (DNGR1), which is known to recognize molecules released from dying cells, might be involved in this process. To investigate this possibility, the team examined atherosclerosis-prone mice that lacked DNGR1—either fully or specifically in bone marrow cells—and showed that these animals had reduced plaque sizes and slower atherosclerosis progression. DNGR1 deletion also led to a dramatic increase in the levels of IL-10—an anti-inflammatory factor—with a concurrent decrease in the number of macrophages within plaques. The team also found that in mice whose bone marrow cells lacked both DNGR1 and IL-10, the protective effects of DNGR1 deletion alone were completely abolished. Altogether, these results indicate that DNGR1, via suppression of IL-10, serves to promote atherosclerosis, and that this necrosis-sensing factor might be a novel therapeutic target for promoting plaque stabilization and slowing atherogenesis.



PVM and A β -Induced Neurovascular Dysfunction (p 258)

Perivascular macrophages mediate amyloid- β driven neurovascular dysfunction, say Park et al.

Alzheimer disease (AD) is the most common form of dementia in the elderly. This debilitating condition is characterized by the intracellular aggregation of tau proteins and the extracellular accumulation of amyloid- β (A β) peptides. It is thought that cerebral vascular dysfunction plays a role in the progression of AD and that A β may be responsible, at least in part, for this dysfunction. Indeed, A β has been shown to disrupt vascular endothelial function and prevent the normal increase in blood flow seen during brain activity. Binding of A β to the receptor CD36 with downstream production of reactive oxygen species (ROS) mediates the vascular dysfunction, but the particular cells involved were unknown. Park and colleagues now suggest that perivascular macrophages may be the culprits. They found that specific depletion of these cells in the brains of AD model mice reduced the oxidative stress and vascular dysfunction caused by A β . They obtained similar results by depleting either CD36 or Nox2 (the enzyme responsible for ROS production) specifically from perivascular macrophages. These results confirm the involvement of CD36 and Nox2 in A β driven neurovascular dysfunction, identify perivascular macrophages as the cellular mediators, and suggest that therapeutic manipulations of these cells may ameliorate brain dysfunction in AD patients.

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