Smad2 and MRTFB cooperate to turn neural crest cells into vascular smooth muscle, report Xie et al.

Proper differentiation of vascular smooth muscle cells (VSMCs) is not only essential for building blood vessels in the embryo, but also in adulthood, where abnormal VSMC differentiation is implicated in atherosclerosis, hypertension, and restenosis after angioplasty. Interestingly, VSMCs derive from 8 different progenitor cell types and exhibit differing characteristics depending on their origins. Xie and colleagues studied the neural crest cell (NCC) derived VSMCs, which ultimately locate to the aortic arch arteries, ascending aorta and carotid arteries. In vitro studies indicate that growth factor TGFβ regulates differentiation of NCC to VSMC, but in vivo experiments have given contrasting results. Xie and colleagues thus turned to a downstream target of TGFβ—Smad2—to resolve the issue. They deleted Smad2 from NCCs in mice and found that while NCCs still migrated to the aortic arch, they failed to differentiate to VSMCs. The VSMC layer in carotid arteries was also diminished. The team also showed that, in a mouse neural crest cell line, Smad2 interacted with transcription factor MRTFB—an important regulator of NCC to VSMC differentiation—which led to upregulation of VSMC markers. The authors therefore suggest that TGFβ signaling, via Smad2, is indeed important for NCC to VSMC differentiation.

Wan et al identify a macrophage receptor responsible for the disposal of dead heart cells after myocardial infarction.

After a heart attack, macrophages gather at the injury site to gobble-up dying cardiomyocytes. This feasting on cellular corpses, or efferocytosis, is essential for efficient resolution of inflammation, which in turn limits the degree of adverse cardiac remodeling and the risk of progression to heart failure. Indeed, it has been shown that defective cardiomyocyte clearance in older mice is associated with impaired heart repair, and that macrophages from older animals exhibit reduced efferocytosis. To learn more, Wan and colleagues examined macrophages with deletions of known efferocytosis receptors. They found only one—MERTK—that was essential for removal of necrotic cardiomyocytes through phagocytosis. They also found that mice lacking MERTK still recruited macrophages to their hearts following myocardial infarction. However, inflammation was slow to resolve, there were more dying and dead cardiomyocytes, infarct size was larger, and heart function was worse. Interestingly, while levels of the MERTK receptor increased in the hearts of wild-type mice 3 to 7 days after a myocardial infarction, the authors also found that some of the MERTK was cleaved into an inactive form. Why this inactivation occurs, whether it worsens with age, and whether it can be prevented to improve recovery after myocardial infarction are all avenues the authors plan to investigate.

Ludewig et al identify an inflammation inhibitor in mice that, after a stroke, limits the breakdown of the blood brain barrier and thus further injury.

After the initial hypoxic insult of an ischemic stroke, the problems are far from over. The resulting tissue damage leads to recruitment of immune cells, which cause inflammation with possible deterioration of the blood brain barrier and further brain damage. Immune cells express adhesion molecules that allow the cells to stick at the injury site and infiltrate the tissue. Blocking certain adhesion proteins has been shown to reduce cerebral damage after stroke in mice. But Ludewig and colleagues hypothesized that blocking the adhesion molecule CEACAM1 might have the opposite effect—because although it is also expressed on immune cells, it suppresses inflammation. They were right: Mice that lacked CEACAM1 fared worse after experimentally induced stroke. Their infarct sizes were larger, they had more pronounced cerebral inflammation, and their motility and neurological performance were more impaired. It turned out that without the anti-inflammatory action of CEACAM1, more immune cells that produced MMP-9—a secreted protease that promoted the breakdown of the blood brain barrier—were recruited to the ischemic brain. Together the results suggest that boosting CEACAM1 or inhibiting MMP-9 might be attractive ways to limit brain damage after stroke.