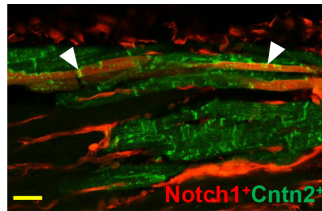


Clonal Expansion of Plastic VSMCs in Disease (p 1313)

Vascular smooth muscle cells vary in their propensity for lesion formation, say Chappell et al.

Vascular smooth muscle cells (VSMCs) in blood vessel walls are generally quiescent, but after a vessel injury, or during the formation of atherosclerotic lesions, these cells contribute to lesion formation by undergoing a phenotypic switch to become proliferative and migratory. However, it is unclear whether or not all VSMCs have equal capacity for lesion formation. To investigate this question, Chappell and colleagues expressed a multicolored reporter specifically in the VSMCs of atherosclerotic mice so that each cell was randomly labeled with one of four colors. The team showed that, in contrast to the multicolored vessel walls, atherosclerotic plaques contained regions that were largely monochromatic—suggesting that they were derived from single cells. These monochromatic plaque VSMCs also displayed a variety of phenotypes, including fibrous cap cells, core plaque cells, and macrophage-like cells. These results suggest that, during atherogenesis, individual VSMCs become highly proliferative and plastic. The team observed similar monochromatic lesions in mice whose vessels were physically injured (by ligation), though the phenotypic diversity of these VSMCs was less pronounced. The authors suggest that targeting the specific subset of highly proliferative VSMCs in vascular disease might curb lesions without adversely affecting healthy vessels.



Notch Regulates Potassium Currents (p 1324)

Khandekar et al discover that Notch signaling regulates potassium channel expression epigenetically.

Cardiac arrhythmias can often arise from anomalies at junctions between the impulse-conducting Purkinje fibers and the cardiomyocytes. Aberrant activation of Notch signaling in the myocardium has been shown to convert cardiomyocytes into Purkinje-like cells and thus disrupt normal junction operations. Khandekar and colleagues, therefore, investigated how Notch signaling prompts this arrhythmia-inducing cell transition. They found that activation of Notch in left ventricular myocytes attenuated potassium currents in these cells, which in turn caused the cells' action potentials to become prolonged—like those of Purkinje fibers. This potassium current suppression was caused by a reduction in the expression of potassium channel subunits, which itself was caused by removal of activating epigenetic marks from the promoters of the subunit genes. The team also showed that, in mice, an increase in Notch activity during heart failure repressed the expression of potassium channels by the same epigenetic means. Thus, targeting Notch signaling may be a potential therapeutic strategy for preventing arrhythmias caused by infarctions or other pathological conditions.



Right VAH

Hypertension and Cerebral Perfusion (p e140)

Warnert et al find evidence supporting the selfish brain hypothesis of hypertension.

High blood pressure affects a quarter of the world's population, but in 95% of these cases, the underlying causes remain unknown. It is clear that, in most patients, increased sympathetic nerve activity (SNA) drives the development of hypertension, but the factors that increase SNA have not been identified. One view is that SNA-induced hypertension is a safety mechanism that ensures sufficient blood flow to the brain. Support for this "selfish brain hypothesis" has come from the finding that, in contrast to other arteries, high resistance in the vertebral arteries of the neck is strongly correlated with hypertension. Moreover, clamping the vertebral arteries of rats increases the animals' SNAs. Warnert and colleagues have now investigated the selfish brain hypothesis in humans. In their study, MRI scans showed that patients with vertebral artery hypoplasia (VAH) were more likely to have frank or borderline hypertension. Importantly, they also showed that, while patients with hypertension tended to have both increased vascular resistance and increased SNA, patients with borderline hypertension tended to have increased vascular resistance alone. This indicates that vascular resistance precedes the increase in SNA. If the selfish brain hypothesis is correct, as these results suggest, then aggressive blood pressure-lowering treatments require more careful consideration, say the authors.

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