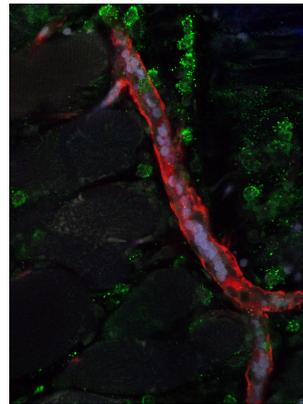


## miR-181b Controls Atherosclerosis and Aneurysms (p 49)

**Di Gregoli et al discover a potential new therapy for attenuating both atherosclerosis and aneurysm.**

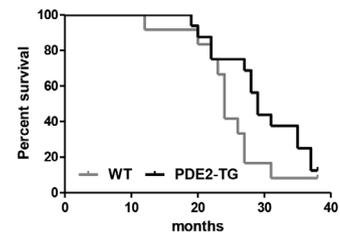
Abdominal aortic aneurysm (AAA) and atherosclerosis, the leading causes of cardiovascular disease, are both associated with increased inflammation and increased degradation of the extracellular matrix. These two pathological features are interrelated as inflammatory macrophages produce matrix metalloproteases (MMPs) and TIMPs that suppress MMP production. Indeed, previous studies have shown that macrophages with low TIMP-3 and high MMP expression are associated with unstable plaques. In liver cancer cells, TIMP-3 has been shown to be suppressed by microRNA miR-181b. Now, Di Gregoli and colleagues report that miR-181b is abundant in both atherosclerotic plaques and AAAs in humans, where it was found to be associated with decreased TIMP-3 expression. The team went on to show that blocking miR-181b activity in mice could retard the development of atherosclerotic plaques and attenuate aneurysm formation. Together, the results suggest that therapeutic suppression of miR-181b could be a novel treatment strategy for slowing or stopping progression of these two potentially deadly vascular conditions.



## Neutrophil AMPK $\alpha$ 2 Controls Vascular Repair (p 99)

**AMPK activation could drive recovery from ischemia in diabetes, say Malik et al.**

Injury-induced limb ischemia is characterized by an initial neutrophil-driven inflammatory phase, followed by monocyte recruitment, angiogenesis, and ultimately resolution of inflammation. Activation of AMPK is thought to play an important role in hypoxia-induced angiogenesis. This enzyme is also known to be dysregulated in diabetes, which is associated with impaired vascular repair and limb ischemia. To examine the relationship between AMPK and limb ischemia more closely, Malik and colleagues studied mice lacking AMPK $\alpha$ 2—the form of the enzyme linked to diabetes. They found that the recovery of blood flow after hind limb ischemia was markedly impaired in these animals, an effect that was fully recapitulated by the deletion of AMPK $\alpha$ 2 specifically from myeloid cells (neutrophils). Deletion of AMPK $\alpha$ 2, from endothelial cells, on the other hand, had no effect on recovery from ischemia. The team determined that the absence of AMPK $\alpha$ 2 in neutrophils caused premature death of the cells, hindering subsequent monocyte recruitment and angiogenesis, while prolonging inflammation. In light of the results, the authors suggest that boosting AMPK in patients with diabetes may help to promote vascular repair and recovery from ischemic injury.



## PDE2 in Arrhythmia and Contractile Function (p 120)

**Vettel et al uncover a potential new strategy for preventing arrhythmia and preserving cardiac function in heart failure.**

After myocardial infarction, the heart works harder to compensate for diminished function. However, this chronic increase in contractility results in hypertrophy, remodeling, and electromechanical dysfunction. As a result, lethal arrhythmias are a common cause of death in heart failure patients. The chronically elevated contractility is driven by prolonged cAMP-mediated  $\beta$ -adrenergic ( $\beta$ -AR) signaling. But heart failure is also associated with increased levels of phosphodiesterase 2 (PDE2), which could, under certain circumstances, degrade cAMP. Whether high PDE2 in heart failure is indeed a mechanism to counteract cAMP is unclear, however. Vettel and colleagues show that overexpression of PDE2 attenuates the rise in cAMP levels in heart cells undergoing chronic  $\beta$ -AR stimulation (to mimic heart failure). Furthermore, overexpression of PDE2 in transgenic mice lowered the animals' heart rates, and protected them from both cardiac function decline and lethal arrhythmias after myocardial infarction. Mice in which PDE2 was pharmacologically inhibited, on the other hand, exhibited increased heart contractility. Together, the results indicate that raising PDE2 levels could be a novel clinical approach for treating heart failure.

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## In This Issue Ruth Williams

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