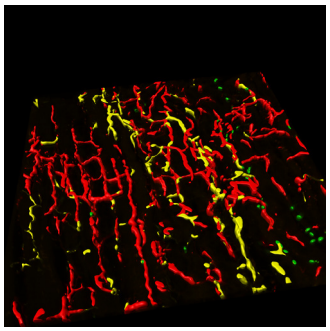
IN THIS ISSUE

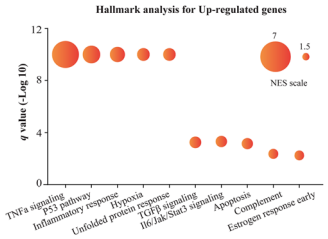
Circulation Research ■ Vol. 122 ■ No. 5 ■ March 2, 2018



Clonal Expansion of Endothelial Cells (p 670)

How blood vessels grow depends on the physiological context, say *Manavski* et al.

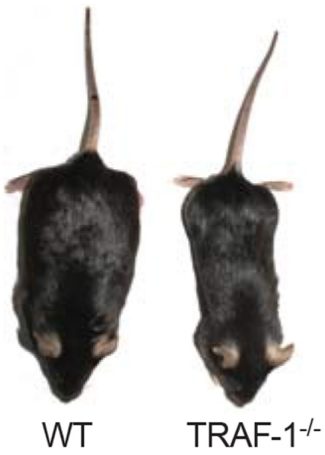
The requirement for new blood vessels is minimal, once human development is complete. However, after tissue ischemia, such as a myocardial infarction, new capillaries grow to restore oxygen to the hypoxic tissue. Manavski and colleagues now show that in confetti mice—animals engineered to have different colored cells for the purposes of lineage tracing—the process of neovascularization differs depending on whether it is a normal part of development or induced via hypoxia. The team found that during normal postnatal retinal angiogenesis in the mice, new blood vessels were formed from the random integration, or mixing, of endothelial cells—evinced by an assortment of different colored cells comprising the vessels. When the animals' retinas were temporarily exposed to hypoxia, however, neovascularization resulted largely from the clonal expansion of endothelial cells (cells of one color dominated). Endothelial cell clonal expansion also drove neovascularization after myocardial infarction and hind limb ischemia in the mice. Knowing how endothelial cells behave during hypoxia could help guide strategies for treating ischemic diseases, as well as prevention of pathological vascularization.



Improved Survival Upon Suppression of FOXO TFs in Laminopathies (p 678)

FOXO transcription factors contribute to cardiac problems in laminopathies, report *Auguste* et al.

Classical laminopathies, such as Emery-Dreifuss muscular dystrophy and Hutchinson-Gilford progeria syndrome, are a diverse collection of disorders caused by mutations to LMNA—a nuclear lamina protein. The wide range of phenotypes associated with laminopathies is thought to reflect both the ubiquitous expression of LMNA and its interactions with chromatin across the genome, which could disturb gene expression in a variety of ways. Despite the diverse manifestations of LMNA mutations, most patients die of dilated cardiomyopathy (DCM), a progressive cardiac dysfunction that leads to heart failure. To examine the molecular mechanisms linking LMNA mutation to DCM, Auguste and colleagues studied gene expression in the hearts of LMNA-deficient mice before the animals showed symptoms of cardiac problems. Of the large number of genes aberrantly expressed, transcription factors of the FOXO family were among the most dysregulated. Moreover, knockdown of FOXO 1 and 3 in the hearts of LMNA-lacking mice almost doubled the animals' survival rate. These results indicate that FOXO transcription factors might be key players in DCM and thus potential therapeutic targets for patients with laminopathy-associated heart failure.



TRAF-1 Dissects Inflammation and Metabolism (p 693)

Chronic inflammation may protect against metabolic pathology in obesity, say *Michel* et al.

Diet-induced obesity is often associated with chronic inflammation and dysregulated metabolic states—such as hyperlipidemia and insulin resistance. This association suggests that metabolic pathologies, that accompany diabetes, may be in part due to chronic low-grade inflammation. However, obesity-related inflammation may not be solely pathogenic, as inhibition of some inflammatory pathways in mice has been found to aggravate obesity or metabolic dysregulation. To examine the role of inflammation in obesity in greater detail, Michel et al studied mice engineered to lack the anti-inflammatory factor TRAF-1 (tumor-necrosis receptor–associated factor 1), which the authors found was upregulated in obese mice and humans. While the TRAF-1 null mice exhibited increased inflammatory cytokine release from adipose tissue with increased immune cell recruitment, the animals did not gain weight on par with wild-type mice when fed a high-fat diet. In comparison with wild-type mice, TRAF-1 null mice also showed improved insulin resistance and greater lipid breakdown. Furthermore, this increased lipolysis was shown to require inflammatory signaling. Together, these results add to the growing body of evidence that in the setting of obesity inflammation is not purely pathogenic, and requires further investigation.

Written by Ruth Williams

(*Circ Res*. 2018;122:639. DOI: 10.1161/RES.0000000000000201.)

Circulation Research
JOURNAL OF THE AMERICAN HEART ASSOCIATION

In This Issue

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Circ Res. 2018;122:639
doi: 10.1161/RES.0000000000000201
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7330. Online ISSN: 1524-4571