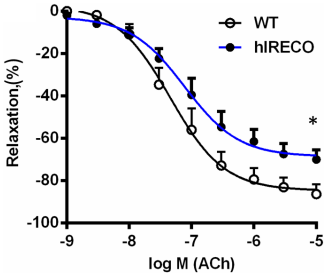
IN THIS ISSUE

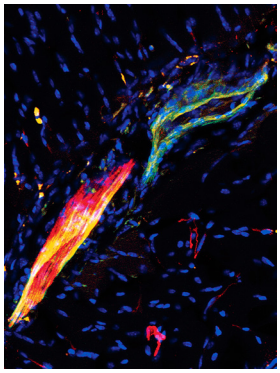
Circulation Research ■ Vol. 120 ■ No. 5 ■ March 3, 2017



Insulin Sensitivity and NO Availability (p 784)

***Viswambharan* et al investigate the effects of enhancing endothelial cell insulin sensitivity.**

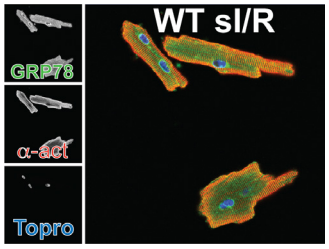
Stimulation of endothelial nitric oxide synthase (eNOS) by insulin increases the production of nitric oxide (NO), which is a suppressor of atherosclerosis. Indeed, insulin resistance in type 2 diabetes is associated with both reduced production of NO and increased risk of atherosclerosis. To find out whether boosting insulin sensitivity in ECs could increase NO production and reduce atherogenesis, Viswambharan and colleagues genetically engineered mice to overexpress the human insulin receptor in ECs. Surprisingly, they found that even though insulin stimulation of the engineered ECs prompted Akt phosphorylation (a downstream mediator of insulin signaling), NO availability was reduced. Instead, insulin stimulation increased the activity of Nox2 NADPH oxidase, which in turn ramped-up production of damaging superoxide. The team then examined the EC-specific insulin receptor over-expression in atherosclerosis-prone mice, and found that the animals were even more prone to atherosclerosis than usual, with significantly accelerated plaque development in their aortas. The study suggests that upregulating insulin signaling may not be necessarily a desirable goal for diabetes treatment.



ER71/ETV2-Mediated Reprogramming of HDF to Ecs (p 848)

***Lee* et al describe a method for generating endothelial cells for therapy, disease analysis, and more.**

Because endothelial cells (ECs) are critical for the repair and growth of blood vessels, researchers have been investigating possible ways to generate ECs for treating vascular disorders and injury. However, adult stem and progenitor cells are poor at endothelial transformation while embryonic or induced pluripotent stem cells, although better at endothelial cell conversion, carry a risk of tumorigenesis. Lee and colleagues, therefore, investigated an alternative idea of converting differentiated somatic cells into endothelial cells directly. Using human postnatal fibroblast cells, the team overexpressed a combination of 7 transcription factors known to be involved in endothelial cell differentiation. They succeeded in converting the fibroblasts into cells whose morphology and gene expression resembled endothelial cells and then, by a process of elimination, discovered that just one of these transcription factors—ETV2—was sufficient for the conversion. The reprogrammed endothelial cells were capable of contributing to vessel formation and recovery from hind limb ischemia in mice. Based on these findings, the authors suggest that direct reprogramming of differentiated fibroblasts into endothelial cells could be used for autologous cell therapies as well as personalized disease studies and drug testing.



ATF6 Links ER Stress and Oxidative Stress (p 862)

Transcription factor ATF6 mitigates oxidative stress as well as ER stress, report *Jin* et al.

The ER stress response of a cell becomes activated when unfolded or misfolded proteins accumulate in the ER. Activating transcription factor 6 alpha (ATF6) is upregulated early in the response and shuttles into the nucleus to activate ER stress genes, which then work to resolve the folding problems. Recently, however, ATF6 has also been shown to protect the heart against ischemia/reperfusion damage. To investigate the mechanism behind this protective effect, Jin and colleagues examined cardiomyocytes lacking ATF6. They showed that on induction of ischemia–reperfusion, the cells produced unusually high levels of reactive oxygen species. ATF6 overexpression relieved this effect. Gene expression analysis revealed that ATF6 activated not only ER stress related genes, but also genes encoding antioxidant proteins, including catalase. The team then showed that when mouse hearts were subjected to ischemia–reperfusion, genetic deletion of ATF6 worsened infarct size and heart function compared to that seen in the wildtype. However, overexpression of catalase restored the ATF6-lacking hearts to wild-type standards. The findings not only identify novel antioxidant target genes for ATF6, but suggest that acute stimulation of ATF6 may be beneficial in protecting against ischemia–reperfusion injury.

Written by Ruth Williams
(*Circ Res*. 2017;120:745. DOI: 10.1161/RES.0000000000000139.)

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Circulation Research
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

In This Issue

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Circ Res. 2017;120:745
doi: 10.1161/RES.0000000000000139
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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