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Apoe<sup>−/−</sup> Cramp<sup>−/−</sup> Apoe<sup>−/−</sup>

**Lack of Neutrophil-Derived CRAMP Reduces Atherosclerosis in Mice**

Döring et al reveal how neutrophils promote atherosclerosis, and suggest a way to stop it.

Atherosclerosis is a chronic inflammatory disorder associated with lipid accumulation in the vessel wall. Although the inflammation is known to be promoted, at least in part, by neutrophils, the precise mechanism by which these cells contribute to atherogenesis remains unclear. When activated, neutrophils release secretory vesicles called granules, and certain granule proteins, such as CRAMP (or LL37 in humans), are able to recruit other inflammatory cell types. To determine whether this happens during atherosclerotic lesion formation, Döring et al examined atherosclerosis-prone mice lacking CRAMP. Sure enough, these mice had fewer inflammatory cells adhering to their blood vessel walls, which resulted in smaller atherosclerotic plaques containing a reduced proportion of macrophages. CRAMP previously has been detected in endothelial cells and macrophages, but the team showed that in atherosclerotic vessels, CRAMP was specifically upregulated in neutrophils. The team also found that CRAMP promotes inflammatory cell recruitment by interacting with their formyl-peptide membrane receptors. Blocking these receptors, or indeed CRAMP activity, may be an avenue toward atherosclerosis therapies, as suggested by the authors.

**Sensing Gene-Regulatory Hyperglycemic Changes by Set7 in Vascular Endothelial Cells**

Histone modifier, Set7, activates proinflammatory genes in response to high blood glucose, report Okabe et al.

Histone proteins in chromatin can be posttranslationally modified in a number of different ways, and these modifications can be indicative of particular states of gene expression. For example, the addition of a methyl group to lysine 4 of histone H3 is associated with gene activation. Okabe et al were studying the activation of proinflammatory genes in response to hyperglycemia and wondered if such H3 methylation might be involved. They examined Set7, an H3-methylating enzyme, and found that when human epithelial cells were exposed to high glucose, the enzyme relocated to the nucleus. There, Set7 activated two proinflammatory genes, IL-8 and HMOX1. However, only IL-8 displayed H3 methylation, suggesting Set7 can activate genes independent of its methylation activity. In mice subjected to transient hyperglycemia, the same gene activation and histone methylation were observed. And, interestingly, the histone modification lasted at least 1 week. This persistence, say the authors, might explain "hyperglycemic memory," the observation that even transient spikes in blood glucose levels can activate pathophysiological pathways leading to diabetes and atherosclerosis.

**Revascularization of Ischemic Skeletal Muscle by Estrogen-Related Receptor-γ**

Transcription factor ERRγ prompts new blood vessel growth in ischemic muscle, report Matsakas et al.

Skeletal muscle ischemia is a common disorder that often accompanies obesity, diabetes, atherosclerosis, and other cardiovascular and metabolic diseases. In severe cases, it can lead to tissue death and limb amputation. Besides adopting a healthier lifestyle, undergoing vascular surgery is among the few available treatment options. Thus, noninvasive treatments are desperately needed. Matsakas et al now suggest that boosting muscle ERRγ levels might be one such noninvasive approach. ERRγ is known to activate a network of proangiogenic and oxidative metabolism factors in mouse skeletal muscle, but whether it could actually promote vascular recovery was unknown. To find out, the team occluded blood vessels in the hind limbs of mice to induce muscle ischemia. Within 1 or 2 weeks, mice that overexpressed ERRγ showed improved revascularization, blood perfusion, and reversal of myofiber damage compared with their wild-type counterparts. The transgenic mice also displayed higher expression levels of proangiogenic factors in the ischemic muscle. The authors suggest that boosting ERRγ levels might be a potential therapy not only for ischemia of the muscle but also for that of the heart or brain.

Written by Ruth Williams.

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