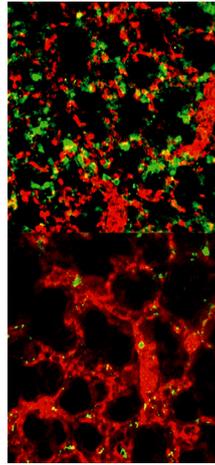


**LKB1 and Atherosclerosis (p 1047)**

**The kinase LKB1 slows foam cell formation and atherosclerosis progression in mice, report Liu et al.**

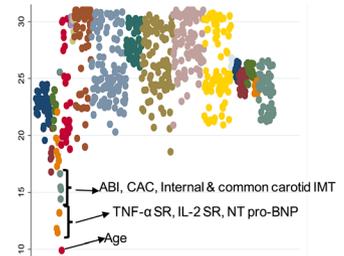
Atherosclerosis begins with the gradual accumulation of fatty deposits on blood vessel walls. Monocytes are recruited to the lesions where they convert to macrophages to phagocytose lipids in the lesions. Continued lipid uptake by the macrophages transforms them into foam cells, which is a critical step in plaque development. However, mechanisms underlying this transformation remain unclear. Liu and colleagues now show that the kinase LKB1, previously identified as having cardioprotective and anti-inflammatory effects, is a negative regulator of foam cell development. They found that, in mice prone to atherosclerosis, the levels of LKB1 in plaque macrophages decreases with disease progression. This decrease prevented LKB1-directed phosphorylation of scavenger receptor A (SRA)—a principle macrophage receptor responsible for lipid uptake and foam cell conversion. The team went on to show that LKB1-directed phosphorylation of SRA promotes the receptor’s degradation. They also found that atherogenesis was accelerated in atherosclerosis-prone mice with LKB1-lacking macrophages. As in mice, levels of LKB1 are also low in humans with atherosclerosis, suggesting the kinase may have a similar role in both mice and humans. Thus, boosting LKB1 levels in macrophages might be a new way to slow or prevent the progression of atherosclerosis.



**Endothelial TRPM2 in PMN Transmigration (p 1081)**

**Mittal et al examine the molecular details of neutrophil transmigration across the vascular endothelium.**

Neutrophils must exit the blood to get to sites of injury or infection, and they do this by squeezing through or between the endothelial cells—a process known as transmigration. Neutrophils generated reactive oxygen species (ROS) for killing bacteria, but recent evidence suggests ROS generation may also help neutrophils exit the blood. Indeed, exposure of endothelial cells in culture to the ROS hydrogen peroxide induces the opening of interendothelial junctions. And this process was shown to require calcium entry into endothelial cells via the cation channel TRPM2. Mittal and colleagues have now investigated this TRPM2-dependent mechanism in mice. The team engineered mice with endothelium-specific conditional deletion of TRPM2 and found that, when the mice were injected with bacterial toxin, the animals exhibited reduced inflammation (fewer neutrophils exiting the blood) compared with wild-type controls. Upon examining the molecular details of TRPM2-dependent transmigration, they found that neutrophil released ROS-induced production of ADPR, a TRPM2 activator, which was essential for the channel’s action. Together, these results suggest that, in cases of excessive inflammation, inhibition of TRPM2 might be an effective anti-inflammatory approach.



**CV Event Prediction by Machine Learning in MESA (p 1092)**

**Machine learning strategy identifies clinical outcome predictors in large epidemiological study, report Ambale-Venkatesh et al.**

Epidemiological studies have led to the identification of several risk factors for cardiovascular disease, such as smoking, high blood pressure, and high cholesterol. But large epidemiological studies can provide many millions of data points from hundreds of variables, making the identification of other risk factors and outcome predictors a complex task. Ambale-Venkatesh and colleagues reasoned that the pattern recognition power of machine learning might make it an effective tool for mining such datasets. The team applied a machine learning technique to data from the Multi-Ethnic Study of Atherosclerosis (MESA), which includes 735 clinical variables (such as imaging, biomarkers, and questionnaires) from 6814 middle-aged to elderly individuals assessed over 12 years. They found that, compared with traditional data-mining approaches, machine learning predicted clinical outcomes with greater accuracy. It also identified nontraditional risk predictors, such as imaging scores, electrocardiography, and serum biomarkers for certain clinical outcomes, as opposed to more traditional predictors, such as ethnicity, gender, and medication use. The authors conclude that machine learning methods may be valuable for linking subclinical disease markers with outcomes in large cohort studies.

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## In This Issue Ruth Williams

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