Monocytosis, Hypercholesterolemia, and the Kinase That Binds Them

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Atherosclerosis is a chronic lipid-driven inflammatory disease that involves the recruitment, infiltration, differentiation, and proliferation of monocytes and monocyte-derived macrophages. In the absence of these cells, disease neither initiates nor progresses. Indeed, leukocytosis is a defining risk factor for increased cardiovascular disease in humans.1,2 Because monocytes are involved in every step of atherosclerosis disease progression,2–4 modifying anything from recruitment to proliferation could significantly affect disease severity. Any modification needs to be extremely precise, however, because the role of monocytes changes as the disease advances. Although recruitment is the underlying culprit during the initial stages,5–7 proliferation becomes consequential later.8 MAPK (mitogen-activated protein kinases), JNK (c-Jun N-terminal kinase), and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) can have widespread effects on cell cycle and cytokine production and may therefore be promising targets in treating complex diseases. Sanz-Garcia et al9 focus on one such kinase, Map3k8, and identify how it can be targeted to alter monocyte biology and atherosclerosis.

See accompanying article on page 237

Map3k8, also known as Tpl2 or Cot, is a mitogen-activated protein kinase involved in activating both mitogen-activated protein kinase and c-Jun N-terminal kinase pathways in humans and mice. The ability to regulate diverse signaling pathways gives Map3k8 a multifactorial role in immune, stromal, and primary tissue cells with ties to proliferation, survival, apoptosis, and cytokine production. As an oncogene, Map3k8 overexpression or mutation also accelerates several types of cancer, including lung, ovarian, colorectal, thyroid, and pancreatic. Map3k8 also plays a role in multiple T-cell–driven autoimmune diseases and is critical for the activation of NF-κB in Th17 cells and for interferon-γ production by Th1 cells.10,11 Despite these known functions in cell cycle regulation and inflammatory cytokine production, the role of Map3k8 in atherosclerosis has not been previously investigated.

Sanz-Garcia et al9 delete Map3k8 to identify how this diverse-acting kinase functions in atherosclerotic plaque formation in a mouse model. The authors use mice lacking Map3k8 and ApoE consuming a high-fat diet for 9 to 10 weeks. To determine whether Map3k8 actions depend on the stromal or hematopoietic compartment, the authors also take advantage of bone marrow chimeras. The authors find that the absence of Map3k8 affects monocyte cell numbers, apoptosis rates, and inflammatory cytokine production. Arguably, the most notable result of Map3k8 deficiency, however, is lower CCR2 mRNA and protein levels in Ly-6Chigh monocytes. CCR2 was implicated in atherosclerosis in 1998 when Boring et al12 showed that Apoe<sup>−/−</sup>Ccr2<sup>−/−</sup> mice had markedly reduced plaque formation compared with Apoe<sup>−/−</sup> controls after only 5 weeks on high-fat diet. Since then, multiple studies have detailed CCR2 role in disease progression. Concordant with the effects of reduced CCR2 levels on Ly-6Chigh monocytes, Sanz-Garcia et al9 find that, after 9 weeks on high-fat diet, Apoe<sup>−/−</sup>Map3k8<sup>−/−</sup> mice develop smaller lesions, with reduced macrophage accumulation and increased staining for smooth muscle cells compared with Apoe<sup>−/−</sup> controls. The authors confirm that these effects are because of Map3k8 loss in the hematopoietic compartment because Apoe<sup>−/−</sup> mice given Apoe<sup>−/−</sup>Map3k8<sup>−/−</sup> bone marrow develop smaller lesions, whereas the opposite occurs in Apoe<sup>−/−</sup>Map3k8<sup>−/−</sup> mice given Apoe<sup>−/−</sup> bone marrow.

Map3k8 involvement in CCR2 expression was first characterized by Rowley et al.,13 who demonstrated that Map3k8 was required for basal expression of CCR2, and, in the absence of Map3k8, monocyte recruitment to the peritoneum after thioglycollate-induced peritonitis was impaired. Sanz-Garcia et al9 take this observation 1 step further using a standard model of atherosclerosis to show that the absence of Map3k8 prevents Ly-6C<sup>high</sup> monocytes from migrating to atherosclerotic lesions and contributing to plaque progression (Figure). Notably, even when Ly-6C<sup>high</sup> monocytes did make it to the aortic endothelium, they did not transmigrate as efficiently, presumably because of increased velocity and lower adhesion rates. It is unclear how all this comes about mechanistically, but there is little doubt about the phenotype.

In addition to suggesting that Map3k8 may be a new target for treating atherosclerosis, this work also contributes to the idea that atherosclerosis is a systemic rather than exclusively local disease. It is true that, once in the plaque, monocytes are influenced by the lipid-rich local environment, where they transform into foam cells and augment inflammation.14 With each study of this kind, however, we are increasingly made aware that multiple events shape the course of disease outside of the vessel wall. A growing body of work on either monocyte production15,16 or recruitment7,17,18 bolsters this paradigm. Collectively, these and other studies paint a picture whereby hypercholesterolemia, monocyteosis, and the atherosclerotic lesion arise from a set of complex interactions in diverse anatomic locations. Accumulation of cells in

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the growing atheroma depends on an arithmetic that must consider monocyte production, recruitment, macrophage differentiation and proliferation, death, and perhaps exit. From Sanz-Garcia et al.\(^9\) it was not entirely clear whether Map3k8 deficiency had a dramatic effect on factors outside of CCR2 expression and Ly-6Chigh monocyte recruitment, but shifting the therapeutic focus from controlling local plaque responses to regulating upstream processes is worth evaluating.

Disclosures

None.

References


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