Atherosclerotic vascular disease is a chronic inflammation characterized by aberrant lipid metabolism and a maladapted inflammatory response. Arterial inflammation is triggered by an insult to the endothelial lining, leading to activation of endothelial cells and recruitment of leukocytes, predominantly monocytes, to the vessel wall. The leukocyte recruitment cascade includes the initial capture and rolling by selectins, chemokine-mediated integrin activation followed by adhesion, transmigration, and directed migration. Through the last decades, several clinical studies and trials have attempted to impede mechanisms of arterial recruitment to abrogate onset and progression of atherosclerosis. Contrary to encouraging results from research in animal models, clinical studies have largely failed. Reasons for such failures include the striking redundancy of cell adhesion molecules and chemokines during atherogenic monocyte recruitment, rendering interference with just one molecule insufficient, prominent off-target effects because of cross-reactivity with receptors of similar structure, and the importance of the targeted molecule in host defense and, consequently, compromised immune responses. With regard to the latter, identification of cell-specific recruitment patterns may pave the way toward novel inhibition strategies with limited side effects.

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In this issue of *ATVB*, Herbin et al show that the lack of the adaptor protein Chat-H (Cas- and Hef1-associated signal transducer hematopoietic isoform) reduces the arterial recruitment of monocytes but does not alter neutrophil recruitment. Previously, Chat-H has been shown to be an important regulator of lymphocyte adhesion, acting upstream of Rap1 (Ras-related protein 1) in the integrin activation pathway. Here, the specificity of monocytes, without compromising neutrophil adhesion, is explained by the lack of expression of Chat-H in neutrophils while it is found abundantly in monocyte subsets. From a mechanistic point of view, the authors use several techniques to prove that macrophage apoptosis and proliferation, both of which are important regulators of macrophage accumulation, are not affected in Chat-H-deficient mice. In addition, macrophage polarization and chemotactic migration are not hampered by the lack of Chat-H, leaving monocyte adhesion and recruitment as major regulator of Chat-H. Indeed, mechanistic studies reveal that Chat-H controls the very late antigen-4 (VLA4)–mediated adhesion of monocytes to vascular cell adhesion molecule 1 (VCAM-1), thus, offering an explanation for the observed phenotype (Figure).

The VLA4-VCAM1 axis is of primary importance during arterial monocyte recruitment. VCAM1 is expressed during early stages of atherosclerosis, and its deletion or therapeutic inhibition in mouse models of atherosclerosis results in greatly blunted lesion development. Although VLA4-VCAM1 stands out as an apparent target for inhibition of atherosclerotic monocyte recruitment, its neutralization has only been approved for treatment of multiple sclerosis and Crohn’s disease. However, natalizumab, a humanized monoclonal antibody toward VLA4 used in multiple sclerosis and Crohn’s disease, predisposes to viral infections of the brain, thus, warranting caution when applied chronically. In addition, the VCAM1-VLA4 axis is crucial during mobilization of myeloid and stem cells from the bone marrow and spleen. Thus, direct interference with the VCAM1-VLA4 axis in the context of atherosclerosis may have various unexpected side effects. In this context, selective neutralization of pathways regulating integrin activity may become an attractive therapeutic target. As an example, annexin A1 was recently shown to prevent chemokine-mediated integrin activation via inhibition of Rap1 phosphorylation. Similarly, growth differentiation factor 15 counteracts chemokine-induced activation of β integrins by interfering with the activity of Rap1-GTPase—both annexin A1 and growth differentiation factor 15 have successfully been used in mouse models of atherosclerosis. Hence, Chat-H may potentially prove to be an additional target to specifically inhibit arterial leukocyte recruitment. To further substantiate its relevance to atherosclerosis therapy, its importance must be evaluated during myeloid cell recruitment in models of acute microvascular inflammation. The environment in large arteries (eg, shear force) may trigger specific intracellular signaling pathways of great relevance to arterial recruitment, such as adhesion strengthening and integrin clustering. The restriction of Chat-H to such signaling would vastly raise its profile as therapeutic target. In addition, recent evidence points toward the crucial role of the simultaneous neutralization of several cell adhesion molecules to override the redundancy of the adhesive cascade. Hence, Chat-H may potentially prove to be an additional target to specifically inhibit arterial leukocyte recruitment. To further substantiate its relevance to atherosclerosis therapy, its importance must be evaluated during myeloid cell recruitment in models of acute microvascular inflammation. The environment in large arteries (eg, shear force) may trigger specific intracellular signaling pathways of great relevance to arterial recruitment, such as adhesion strengthening and integrin clustering. The restriction of Chat-H to such signaling would vastly raise its profile as therapeutic target. In addition, recent evidence points toward the crucial role of the simultaneous neutralization of several cell adhesion molecules to override the redundancy of the adhesive cascade.
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Disclosures

None.

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