Folate Receptor: A Macrophage “Achilles' Heel”?

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Cardiovascular diseases are the most common cause of death worldwide. Atherosclerosis, the underlying inflammatory disease, develops through the progressive accumulation of lipids and leukocytes in the vessel wall. Over the past 30 years, lesional macrophages have emerged as central inflammatory orchestrators of disease progression and its complications. Macrophage precursors, the circulating monocytes, invade predilection sites of dysfunctional endothelium, differentiate, and engulf lipids. Lesional macrophages secrete cytokines, chemokines, growth factors, and lytic enzymes that promote plaque destabilization and rupture, which lead to myocardial infarction and stroke. Interference with monocyte recruitment and macrophage accumulation reduces lesion burden in experimental models, which suggests that such approaches could be beneficial in human disease.

Much of current cardiovascular disease management focuses on treatment of known risk factors such as high cholesterol. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, the class of drugs known as statins, lower cholesterol but also can exert atheroprotection by targeting inflammation. Treatment of atherothrombotic disease by direct and specific targeting of inflammation is being investigated, and clinical trials with low-dose methotrexate and anti–interleukin-1β are under way. Although these studies are exciting, previous work reminds us that antinflammatory approaches require caution. Indiscriminate blockade of CD40L showed promise in several experimental studies, but clinical trials had to be aborted because of thromboembolic complications. More selective inhibition of the interaction of CD40L with integrin Mac-1, however, impaired atherogenesis without affecting thrombus formation. The example illustrates that strategies aimed at targeting inflammation should be considered in their immunophysiological and molecular contexts.

In this issue of the Journal of the American Heart Association, Furusho et al endeavor to treat atherosclerosis by targeting and killing lesional macrophages with an anti–folate receptor β (FRβ) immunotoxin. Macrophages upregulate FRβ during inflammation. Peritoneal murine macrophages, for example, upregulate FRβ in response to challenge with thioglycollate, zymosan, or bacteria, and macrophages in rheumatoid arthritis and pulmonary fibrosis express functionally active FRβ that can be targeted therapeutically in an experimental setting. The idea for the study by Furusho et al was therefore simple. If lesional FRβ-expressing macrophages are atherogenic, then delivery of a recombinant immunotoxin (a truncated Pseudomonas exotoxin A [PE38] conjugate that kills the infected cell) to those macrophages should be atheroprotective. The anti-FRβ immunotoxin was meant to achieve 3 aims: to target FRβ-expressing cells, to facilitate internalization of the toxin in those cells, and, by implication, to minimize adverse effects of the toxin on bystander, non–FRβ-expressing cells.

Although others have shown in animal models that lesional macrophages upregulate the folate receptor, Furusho et al are the first to target increased FRβ expression on lesional macrophages therapeutically. The authors provide evidence by immunohistochemistry and immunofluorescence that FRβ is expressed by 60% to 70% of CD68-positive lesional macrophages but not by T cells, endothelial cells, or smooth muscle cells. The authors report on FRβ expression in human carotid artery plaques and show that treatment of mice with anti-FRβ immunotoxin decreased lesional macrophage content compared to controls. This reduction in cell number was associated with a reduction in percent lesion area. Importantly, differential blood cell counts did not change in the anti-FRβ immunotoxin group, which suggests a mechanism that is localized and presumably limited to the plaque. Indeed, the authors reported increased cell death in lesions, lending further support that the anti-FRβ immunotoxin acted locally.

Is the study convincing? The effects of the immunotoxin on CD68-positive macrophages are striking, but it is not yet
Figure 1. Proposed model of immunotoxin-mediated killing of FRβ-expressing macrophages in atherosclerotic lesions. The immunotoxin consists of a recombinant, biologically active fragment of *Pseudomonas* exotoxin A (PE38) that is linked to the disulfide-stabilized variable region fragment (dsFv) of a monoclonal antibody (mab) against FRβ. Upon binding to FRβ on lesional macrophages, the immunotoxin is internalized and intracellularly processed, leading to toxin-mediated adenosine triphosphate–ribosylation and inactivation of elongation factor 2, inhibition of protein synthesis, and cell death. Elimination of FRβ-positive macrophages reduces atherosclerosis. Vh indicates variable region of the light chain; VH, variable region of the heavy chain; and FRβ, anti-folate receptor β.

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None.

References

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