The S100A8/A9 complex (also known as myeloid-related protein-8/14 or calprotectin) is a heterodimer, comprising S100A8 and S100A9, which has intracellular and extracellular roles in modulating calcium signaling, arachidonic acid metabolism, and inflammatory activation of leukocytes through innate immune signaling pathways. S100A8/A9 is expressed predominantly by granulocytes; however, there is emerging evidence that platelets, smooth muscle cells, and cardiac myocytes express this complex. In resting cells S100A8 and S100A9 are retained in the cytoplasm, but following cell activation the S100A8/A9 complex translocates to the cell surface, is secreted, and circulates in plasma.

**Article p741**

S100A8/A9 has been implicated in the pathobiology of inflammatory disorders, such as inflammatory bowel disease, rheumatoid arthritis, and transplant rejection, and because S100A8/A9 plasma levels increase during inflammation, the molecule has shown promise as a biomarker for disease activity. The discovery that S100A8/A9 might be involved in the inflammatory pathobiology of atherosclerosis and cardiovascular (CV) disease arose out of a transcriptional profiling investigation looking for novel regulators of atherothrombosis in which S100A9 expression was increased in the platelets of patients with acute plaque rupture and ST-segment elevation myocardial infarction (MI) compared with patients with stable angina and nonthrombotic coronary artery disease (CAD). Subsequent studies demonstrated that plasma S100A8/A9 serves as a biomarker of CV risk, predicting rates of MI, stroke, and CV death in apparently well individuals and in survivors of acute coronary syndromes (ACS). S100A8/A9 is highly expressed at sites of coronary artery thrombosis and because plasma levels of S100A8/A9 increase prior to markers of myocardial necrosis, the molecule is a promising candidate biomarker for the detection of unstable plaques in the management of ACS.

Despite serving as a clinical CV biomarker, it was initially unclear whether S100A8/A9 is simply a marker of inflammation or whether it regulates the inflammatory processes that promote atherosclerosis and contribute to pathological responses during acute MI. In this issue of the Journal, Katashima et al report enhanced expression of the S100A8/A9 complex in acute MI patients. In serial measurements, S100A8/A9 serum levels were consistently 1.5- to 2.0-fold higher in patients presenting with acute MI (n=55) compared with those presenting with unstable angina pectoris (n=16). Immunohistochemical analysis also demonstrated that infiltrating neutrophils and macrophages express high levels of S100A8/A9 at the site of acute MI. These results do not demonstrate causality, nor can we assess whether overexpression of S100A8/A9 precedes rather than follows the acute insult. Yet these observations support a role for S100A8/A9 in the pathophysiology of acute MI. Considerable current interest concerns the role of innate immune receptors in atherosclerosis and CAD, and it would also be of interest to know whether S100A8/A9-expressing cells have increased expression of toll-like receptor 4 (TLR-4), which is an innate immune receptor that binds S100A8 and activates inflammatory leukocyte signaling pathways, or whether S100A8/A9 expression associates with monocytes bearing the markers of the proinflammatory subset, including high relative expression of CD14, a coreceptor for TLR-4 signaling, or P-selectin glycoprotein ligand-1, a molecule that directs leukocyte adhesion to platelet-rich arterial thrombi through interaction with the platelet adhesion molecule, P-selectin.

Taken in context, increased expression of the S100A8/A9 complex at sites of coronary thrombosis during acute MI provides a mechanism for the amplification of proinflammatory signals. Intracellular S100A8/A9 facilitates leukocyte arachidonic acid trafficking and metabolism, and S100A8/A9 plays a critical role in calcium-regulated cytoskeletal reorganization during transmigration of phagocytes. Extracellular S100A8 binds TLR-4 on leukocytes and results in activation of nuclear factor-κB-regulated inflammatory responses and increased expression of tumor necrosis factor-α. In addition to regulating leukocyte activation responses, S100A8/A9 also controls leukocyte trafficking during inflammation. Neutrophils and monocytes treated with S100A8/A9 increase their expression and activation of the leukocyte integrin adhesion molecule, Mac-1, and studies in S100A8/A9-deficient mice demonstrate that S100A8/A9 regulates leukocyte migration into inflamed tissues. Clinical correlations among S100A8/A9, Mac-1 expression, and leukocyte adhesion exist in diabetic patients, in whom elevated serum levels of S100A8/A9 correlate with increased expression of Mac-1 on peripheral blood monocytes and enhanced monocyte adhesion to extracellular matrix proteins through Mac-1.
The S100A8/A9 complex is highly expressed in human and mouse atherosclerotic lesions,15,17 and S100A8/A9-expressing monocytes preferentially infiltrate atherosclerotic lesions compared with S100A8/A9-negative cells.17 S100A9 expression in human atherosclerotic plaques coincides with heightened inflammation and morphological features associated with plaque rupture.18 Recent investigations demonstrate that S100A8/A9 promotes vascular inflammation and regulates leukocyte and smooth muscle cell inflammatory and proliferative responses during vascular injury.19 S100A8/A9-deficient mice have smaller atherosclerotic lesions, less atherosclerotic plaque inflammation, and decreased vasculitic and angioplasty restenotic responses.20 Mechanistically, deficiency of S100A8/A9 offers protection from vascular injury by blunting activation of macrophage and neutrophil inflammation pathways and by decreasing leukocyte accumulation in inflamed tissues.21

It is increasingly evident that in addition to being a biomarker of inflammation and CV risk, S100A8/A9 is also an important regulator of atherogenic processes. Less, however, is understood about the role of this molecule in the inflammation and tissue repair pathways that follow atherothrombosis and acute MI. Robust leukocyte expression of S100A8/A9 at sites of MI implies a potential role for this molecule in the responses that influence reperfusion injury and myocardial remodeling, but further investigation is required to determine whether S100A8/A9 plays an important regulatory role in pathogenic or repair processes following acute MI.

Acknowledgments

This work was supported in part by grants from the National Heart, Lung, and Blood Institute to Dr Croce (1K08HL086672), a Michael Lerner Young Investigator Award to Dr Croce and a Harris Family Foundation Young Investigator Award to Dr Croce.

Disclosures

The author reports no significant conflicts of interest related to the content of this publication.

References