LETTER

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New Coronary Heart Disease Risk Factors: The Dark Side of the Moon

To the Editor:

We appreciate your Commentary "New Coronary Heart Disease Risk Factors."[1] In accordance with your observation that systemic inflammation and related various diseases represent a new risk factor, we are pleased to underline our experience in this field.

Previous observations documented that CD11b/CD18 is a well-known surface receptor to mediate cellular inflammatory responses on neutrophils and monocytes/macrophages. CD11b/CD18 may promote the adhesion of neutrophils and monocytes/macrophages to the endothelium, as the inflammasome. Like all integrins, CD11B/CD18 integrin is an adhesion molecule in which a common $\beta 2$ subunit is noncovalently associated with an α L subunit. The metal-ion−dependent adhesion site, a short amino-acid motif within the I domain, is most likely where the CD11B/CD18 integrin interacts with intercellular adhesion molecule (ICAM)-1. The proinflammatory cytokine interleukin (IL)6 promote the adhesion of inflammatory monocytes to endothelium mediated by ICAM, and interaction between platelets, to favor thrombosis.[2,3]

Thirty years ago, I underlined the role of increased expression of adhesion molecules of neutrophils and monocytes in unstable angina.[4] In an editorial in the same issue of *Circulation*, Entman and Ballantyne[5] supported my hypothesis of the role of inflammation in atherosclerosis and cardiovascular diseases. Inflammation and thrombotic events are frequently observed, as reported in the Commentary,[1] in patients affected by gout, inflammatory bowel disease, autoimmune collagen vascular disease, and psoriatic arthritis. Neutrophils and monocytes/macrophages are an active part of these diseases to induce thrombosis and hemostasis cascade, but their role has not yet been sufficiently explored in the pathologies with systemic inflammation. Previous observations documented that inflammation mediated by phagocytes in rat lungs is blocked by preincubation with anti-Mo1 monoclonal antibodies (heterodimeric glycoproteins expressed on the plasma membrane of neutrophils, monocytes, macrophages, and a subset of large granular lymphoid cells), thus preventing pulmonary injury.[6] These antibodies react with CD11b/CD18 integrin complex, which represents a major adhesion molecular structure on neutrophils and monocytes/macrophages to link ICAM on the endothelium. Moreover, IL6 promotes the adhesion of inflammatory monocytes to the endothelium through the interaction with ICAM, also acting on platelets, to favor thrombosis.[3,7]

Activated monocytes release IL1, which induces biosynthesis and cell surface expression of procoagulant factors and enhances platelet aggregation and activation. Platelet activation seems, in turn, to help neutrophil accumulation within inflammatory sites; the CD11B/CD18 interacts with platelets, fibrinogen, and factor X.[7,8] Therefore, as has also been reported in ischemic diseases and unstable angina,[3] activated leukocytes and platelets potentiate each other's effects, favoring the occurrence of thrombosis. In addition, Altieri and Edgington[9] described the binding of soluble clotting factor X to CD11b/CD18. Fibrinogen and factor X effectively compete with each other and with C3bI for binding to CD11b/CD18, suggesting spatial proximity or identity in the binding sites involved. The physiological significance of factor X and fibrinogen binding with activated CD11b/CD18 in vivo is one of the possible bridges between inflammation and thrombosis. The demonstration that CD11B/CD18 interaction with endothelial ICAM is responsible for inflammation and thrombosis and plays a key role in cardiovascular disease, is supported by data on the use of iloprost analog of prostacyclin.[10] In vivo, this drug modifies the expression of the CD11B/CD18 of phagocytes[11,12] that have a key role in leukocyte-endothelium interactions in cases of inflammation and thrombosis. In fact, in clinical use to prevent cardiovascular events in patients with connective diseases, scleroderma patients who received this flexible IV iloprost regimen achieved clinical improvement, and reduced cardiovascular diseases and renal crisis.[13,14] In patients with lower limb ischemia such as claudication or acute critical ischemia, iloprost as an adjuvant to surgery significantly reduced mortality and overall major event rate.[15,16]

Neutrophils and monocytes of atherosclerosis and scleroderma patients showed a significant decrease in the expression of the CD11B/CD18 adhesion receptor after 6 hours of iloprost infusion.[11] Neutrophils and monocytes

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Requests for reprints should be addressed to Antonino Mazzone, MD, Department of Internal Medicine, ASST Ovest Milanese, Legnano Hospital, Via Papa Giovanni Paolo II, 20025 Legnano (MI), Italy.

E-mail address: antonino.mazzone@asst-ovestmi.it

released a lower amount of anion superoxide (O_2^-) after 6 hours of iloprost treatment. These data confirm other clinical observations that inflammation endothelial dysfunction and thrombosis are linked by the interaction of CD11B/CD18, with ICAM, fibrinogen, factor X, and platelets. Finally, statins, a very important drug in this field, inhibited CD11B/CD18 integrin.[17] This inhibition by statins was specific, and in part explains the anti-inflammatory action of these molecules that block the interaction between monocytes to endothelium via ICAM.[18]

These mechanisms in diseases with systemic inflammation, and the use of biological drugs to modify these aspects, need new research to explain new coronary risk factors and clinical impact on the outcome.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Antonino Mazzone, MD
Nicola Mumoli, MD
Department of Internal Medicine, Legnano and Magenta Hospitals, ASST Ovest Milanese, Legnano, MI, Italy

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