Osteopontin is an arginine-glycine–aspartate (RGD) containing adhesive glycoprotein first identified in bone but subsequently detected in many other tissues, including, dentin, cartilage, kidney, and vascular tissues.1-3 It is expressed by a wide variety of inflammatory cells (eg, macrophages, T lymphocytes, NK cells), and, to a lesser extent, by endothelial cells and smooth muscle cells. The RGD domain facilitates tissue binding of osteopontin to various extracellular matrix proteins, such as αβ1 integrin and fibronectin. Additionally, osteopontin may engage CD44 through an RGD-independent mechanism. In extracellular fluids, osteopontin functions as a cytokine, and its plasma levels are increased in autoimmune diseases such as lupus, rheumatoid arthritis, and multiple sclerosis.4 The diverse biological actions of osteopontin could potentially regulate many processes pertinent to vascular disease, including inflammation, cell adhesion, viability, angiogenesis, and calcification (Figure).5-6 Such actions may underlie its presumed role in the pathophysiology of atherosclerosis and in modulating arteriopathy associated with diabetes and chronic renal failure (reviewed by Johnson et al7). Of relevance to the present topic, Bruemmer et al reported that deletion of osteopontin reduced formation of abdominal aortic aneurysms (AAA) in mice infused with angiotensin II.8

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Conceptually, it is logical to presume that osteopontin would contribute to the pathogenesis of AAA. First, in experimental models and in humans, AAA are characterized by extensive inflammatory cell infiltration and induction of proinflammatory cytokines.9-12 Osteopontin can positively regulate these processes through several mechanisms. Second, the inflammatory milieu of AAA is associated with activation of matrix metalloproteinases (MMPs) that contribute to weakening of the aortic wall and aneurismal dilation.11,13-15 The MMPs most strongly implicated in human AAA are matrix metalloproteinase (MMP)-2 and MMP-9, and osteopontin was demonstrated to upregulate the activity of these proteases in vitro and in vivo.16,17 Furthermore, accumulating evidence suggests that oxidative stress plays an important role in AAA (reviewed by McCormick et al18), and osteopontin can serve both as a transducer and amplifier of oxidative stress.19-21 Interestingly, osteopontin may upregulate MMP-9 through induction of oxidative stress, suggesting a mechanism linking these pathophysiological events to the development of AAA.21

Experience cautions us, however, that in complex biological diseases such as AAA, dissecting out the role of inflammatory mediators is often not as straightforward as might be presumed. Inflammation is a complicated process involving a myriad of interactive factors whose levels may fluctuate spontaneously and in response to extrinsic factors. Plasma levels of inflammatory cytokines may not correlate with levels present in vascular tissues, and tissue levels may be subject to both temporal and spatial variation. In addition, the proinflammatory properties of many cytokines, including osteopontin, are, to some extent, offset by antiinflammatory actions.5 It is with these caveats in mind that one should interpret the study by Golledge et al in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology.22

In their study, Golledge et al examined the association between osteopontin and AAA using several approaches. First, they measured serum levels of osteopontin in two groups of patients: one group undergoing screening for AAA, and another group with documented vascular disease referred to a tertiary care center for management. Second, they assayed levels of osteopontin in aortic tissue samples of patients with and without AAA. Finally, they examined the association between selected single nucleotide polymorphisms (SNPs) of the osteopontin gene and AAA. The authors are to be commended for taking such a comprehensive approach in this study.

In both the screening and referral groups, serum osteopontin levels were independently associated with the presence of AAA after adjusting for other risk factors. Interestingly, C-reactive protein (CRP) levels were independently associated with AAA in the screening group, but not the referral group. It is notable that CRP levels were much higher in patients in the referral group (with or without AAA) than in the screening group, which likely reflects the increased burden and complexity of atherosclerosis, and the higher frequency of risk factors such as diabetes and cigarette abuse, in patients referred for tertiary management of vascular disease. Moreover, in patients from both groups with small AAA who were followed for 3 years with serial ultrasound studies, initial osteopontin levels predicted AAA growth after adjustment for other risk factors. Collectively, these data suggest an association between osteopontin and human AAA and raise the possibility of a causal relationship.
Overview of potential mechanisms whereby osteopontin may bind to extracellular matrix proteins (eg, integrin) and adhesion molecules (eg, CD44) to regulate vascular disease.

If osteopontin is indeed a mediator of human AAA, one might expect serum levels to be higher in subjects with larger versus smaller AAA. This was not the case, as osteopontin levels were virtually identical in referral patients with 30- to 49-mm (diameter) AAA as compared with 50- to 80-mm AAA. Because circulating osteopontin levels may not reflect the levels present in AAA, the authors also measured osteopontin in aortic tissue samples. Interestingly, osteopontin levels were higher in small AAA (30 to 50 mm) as compared with large AAA (>50 mm) or non-aneurysmal aorta (<30 mm). The authors postulate from these results that osteopontin contributes to the early development and progression of AAA. Perhaps at later stages of the disease, osteopontin levels in AAA decline as tissue degeneration becomes more pronounced and calcification ensues. Although this is certainly possible, alternative explanations merit consideration. First, medications and renal function status could have influenced serum and/or tissue osteopontin levels in the study patients. In this regard, atorvastatin therapy (20 mg/d) was reported to reduce plasma osteopontin levels in hypercholesterolemic patients. Also, angiotensin II is a potent inducer of osteopontin expression, so plasma and tissue levels of osteopontin might have been influenced by the use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Although medication usage was not recorded in this study, it is possible that statins, ACE inhibitors, and/or ARBs were prescribed more frequently and/or at higher doses in patients with large versus small AAA, thereby spuriously lowering osteopontin levels in patients with large AAA. Likewise, data regarding renal function were not included in the study, even though impaired renal function was reported to upregulate osteopontin expression (reviewed by Moe).

Several other practical points need to be considered in interpreting data from this study. First, the serum osteopontin levels were derived from a single assay in each patient. Because osteopontin levels in serum of patients with AAA might vary over time, a single assay may not be indicative of the cumulative burden of expression. Second, tissue osteopontin was assessed in biopsies of the anterior aortic wall opposite the inferior mesenteric artery. It is possible that different results would have been obtained had other locations, such as the aneurysm neck, been assayed. Finally, it is conceivable that osteopontin has neutral, or even inhibitory, effects on AAA formation or progression in humans. In the latter case, upregulation of aortic osteopontin could function as a homeostatic mechanism, the loss of which might actually contribute to disease progression.

In a subset of patients in the screening group, the investigators examined the association between 5 selected SNPs of the osteopontin gene and AAA. No associations were detected between any of the SNPs and presence or growth of AAA. Moreover, the investigators were unable to demonstrate that the selected SNPs were associated with altered levels of serum osteopontin, as had been reported in prior studies. This apparent discrepancy may be attributable to inherent differences in demographics and medical conditions of the study patients. Also, as the authors point out, AAA is a complex disease that is influenced by both genetic and environmental factors. Further studies will be required to determine whether these and/or other SNPs of the osteopontin gene are associated with AAA in certain subsets of patients.

In conclusion, osteopontin is an attractive candidate mediator of human AAA. The study by Golledge and colleagues demonstrates that serum osteopontin levels are independently associated with presence and growth of AAA in humans. Whether osteopontin can best be classified as a biomarker, mediator, or modulator of human AAA, however, remains to be determined.

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Disclosures
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Mazen Shaheen and Neal L. Weintraub

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