Bone Sialoprotein and the Paradox of Angiogenesis Versus Atherosclerosis

Chunming Dong, Pascal J. Goldschmidt-Clermont

Bone sialoprotein (BSP) is a protein thought to be highly specific for bone. BSP contains an arginine-glycine-aspartic acid (RGD) cell attachment sequence involved in osteoclast adhesion to bone matrix via the vitronectin receptor and plays an important role in the early process of bone mineralization and resorption. The study by Bellahcene et al1 in this issue of Circulation Research indicates that BSP mediates adhesion and chemotactic migration of endothelial cells and promotes angiogenesis, suggesting that BSP may be an important factor in angiogenesis and the initiation of atherosclerosis, two processes that are probably related.

In earlier studies, Folkman2 hypothesized that tumor growth beyond a few millimeters requires recruitment and growth of a new microcirculation, or angiogenesis, which is induced by tumors as lifelines for oxygen and nutrients. New blood vessels also provide exits for cancer cells to spread to other parts of the body. Angiogenesis is also involved in physiological conditions, such as embryogenesis, and other pathological conditions, such as wound healing. The process of angiogenesis requires a highly coordinated series of events, including endothelial cell proliferation, migration, tube and lumen formation, and, in some cases, recruitment of smooth muscle cells (SMCs) and other adventitial cells.

Adhesive interaction of cells with components of the extracellular matrix is a recognized requirement for cell proliferation and migration. Evidence indicates that many of the adhesive interactions are mediated by members of the integrin family of heterodimeric adhesion receptors. Among these integrins, α3β1, which is expressed by a variety of cell types, has been shown to play a key role in the cell migration involved in metastasis and angiogenesis.3 The work presented by Bellahcene et al1 indicates that BSP, a bone-associated protein that contains the RGD sequence, a common recognition sequence for most integrins, binds α3β1 in endothelial cells and mediates the migration of such cells, extending the study by Byzova et al.4 Furthermore, Bellahcene et al1 show that another integrin, αvβ3, does not bind BSP, suggesting that there is a certain degree of specificity for the interaction between BSP and α3β1.

The in vivo data indicating that BSP promotes angiogenesis via its interaction with α3β1 integrin and that such an angiogenic effect is probably even greater than that of basic fibroblast growth factor (bFGF)5 are intriguing. These data underscore the physiological and pathophysiological consequences of the interaction between BSP and α3β1 integrin and define BSP as a novel angiogenic factor. These findings may provide an explanation for the previously established association of BSP expression levels in tumors with the development of bone metastases.5 Higher BSP expression in the tumor correlates with an increased risk of metastasis of carcinomas to bone tissue, which could be due to angiogenesis enhancement by BSP. In addition, BSP expression in the tumor may facilitate tumor cell migration and calcification.

Several families of factors have been implicated in angiogenesis. These include angiogenic factors, such as vascular endothelial growth factor (VEGF) or bFGF, and antiangiogenic factors, such as angiostatin or endostatin.6 Translational research has now been initiated by several centers to test the hypothesis that local delivery of angiogenic agents, especially VEGF and bFGF, by various strategies, including viral vectors, naked DNA, or purified recombinant proteins, may improve blood flow to ischemic tissues in patients with advanced atherosclerosis.7 Similarly, clinical trials for local delivery of antiangiogenic factors, such as angiostatin, using various techniques, are underway to treat patients with malignant tumors.8 Although blockade of BSP interaction with α3β1 may limit tumor growth and metastasis, the effect of local delivery of BSP to improve blood flow to ischemic tissues, in particular the myocardium, may be complicated by the fact that BSP-α3β1 interaction may also initiate and aggravate atherosclerosis.

Neointima formation, associated with both atherosclerosis and restenosis, is a complex process that involves SMC migration and proliferation. The molecular mechanisms governing intimal thickening have been a focus of intense research. Numerous studies have indicated a critical role for integrin heterodimers, including α3β1, in mediating cell-matrix interactions and SMC adhesion and migration, implicating the potential involvement of physiological ligands containing RGD sequence, including BSP, for the activity of such integrins.9 Indeed, in vitro studies have shown that osteopontin, a bone-associated protein closely related to BSP, which contains the RGD sequence, supports SMC adhesion to α3β1, α5β1, and αvβ3 integrins and mediates SMC migration specifically via αvβ3.9 In vivo experiments have demonstrated that osteopontin and αvβ3 are expressed in vascular SMCs. In addition, osteopontin expression is upregulated in human atherosclerotic and restenotic lesions.10 Using animal models of neointima formation, several groups have observed increased expression of osteopontin and αvβ3 in such lesions.11 More direct evidence supporting the potential

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role of osteopontin in the process of intimal thickening stems from the observation that neutralizing antibodies to osteopontin limit neointimal thickening in rat carotid artery after balloon injury.\textsuperscript{12} RGDF and \( \alpha \beta_3 \) antagonists have been shown to inhibit neointima formation in rabbit, hamster, porcine, and guinea pig vascular injury models, an effect that has been interpreted to be mediated via the disruption of osteopontin-\( \alpha \beta_3 \) interaction.\textsuperscript{13,14} The data presented by Bellahcene et al.,\textsuperscript{1} showing that BSP interaction mediates endothelial cell adhesion and migration, implicate the potential role for BSP in atherosclerosis. It is probable that BSP-\( \alpha \beta_3 \) interaction is disrupted by RGDF and \( \alpha \beta_3 \) antagonists, which may account for, at least in part, the antiatherogenic effect exerted by these agents in the in vivo experiments. Characterization of BSP-\( \alpha \beta_3 \) interaction and such interaction-induced adhesive and migratory effect on SMCs, examination of BSP expression in vascular lesions, and the use of neutralizing antibodies to BSP in animal models will help clarify the putative role of BSP in the initiation of atherosclerosis and may provide a therapeutic alternative to vascular disease.

Calcification associated with atherosclerotic plaques has been increasingly recognized as an active, regulated process that contributes to the fate of the atherosclerotic plaque, including rupture and subsequent thrombosis.\textsuperscript{15} However, the molecular determinants regulating extracellular matrix calcification have yet to be identified. Several studies have shown that noncollagenous bone matrix proteins related to BSP, such as osteonectin, osteocalcin, and osteopontin, are found in atherosclerotic vessels and may regulate dystrophic calcification.\textsuperscript{16} A recent study has shown that BSP is expressed together with osteonectin, osteocalcin, and osteopontin by vascular pericytes.\textsuperscript{17} Further study is required to examine the expression of BSP and its spatial relationship with early calcification in atherosclerotic plaques to establish the role for BSP in vascular calcification.

The elegant study by Bellahcene et al.\textsuperscript{1} reveals a novel function of BSP as an angiogenic factor. It also opens new research venues to study the role of BSP in the initiation and calcification of atherosclerosis. The relationship between BSP as an angiogenic factor and a factor promoting atherosclerosis or neointimal hyperplasia does not appear to be unique to BSP. It has been shown that microvessels within the advanced atherosclerotic lesions have a high level of VEGF expression. Moreover, intense VEGF expression is noted in totally occlusive lesions with extensive neovascularization.\textsuperscript{18} The angiogenic factor bFGF may incite, in some instances, aggressive vascular neointimal proliferation.\textsuperscript{19} Furthermore, anti-angiogenic factors can reduce substantially neointimal formation in animal models of atherosclerosis.\textsuperscript{19} The dual role of molecules implicated in angiogenesis and atherosclerosis stresses the challenge to scientists seeking a way to promote angiogenesis for ischemic tissues. The success of such efforts will likely require the fine characterization of molecular pathways involved in both angiogenesis and atherosclerosis. Until these pathways are characterized, one might be concerned about progression of atherosclerosis when using angiogenic factors such as BSP, VEGF, or bFGF to treat ischemic heart disease. Although the participation of factors in processes like angiogenesis and atherosclerosis may appear paradoxical, our evolving understanding of advanced atherosclerosis as a misguided form of angiogenesis provides a new target for the design of therapeutic strategies.

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