Endothelium-Derived Bone Morphogenic Protein Antagonists May Counteract the Proatherogenic Vascular Effects of Bone Morphogenic Protein 4

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In the present issue of *Circulation*, Chang et al report novel shear stress–sensitive paracrine mechanisms that regulate the activity of bone morphogenetic proteins (BMPs) in the vascular wall. BMP2 and BMP4 are structurally related members of the transforming growth factor-β superfamily. Recent studies demonstrated that vascular endothelial and smooth muscle cells are a significant source of BMPs, which regulate a host of cellular functions, including cardiovascular development, and neovascularization in tumors, and smooth muscle cell chemotaxis in response to vascular injury, and control the balance between proliferation and activation of apoptosis in pulmonary arterial endothelial and smooth muscle cells.

Many lines of evidence suggest that BMPs may function as proinflammatory, prohypertensive, and proatherogenic mediators in the vessel wall. Recent studies have demonstrated a striking upregulation of BMP2/4 in atheroprotective vascular regions and atherosclerotic lesions, and hypotheses have been put forward that endothelium-derived BMPs contribute to vascular calcification (reviewed elsewhere). In vitro, BMP2 and BMP4 were shown to exert proinflammatory effects. Activation of BMP signaling by either overexpression of BMP2/4 in vascular cells or administration of recombinant BMPs activates NAD(P)H oxidases, which results in cellular oxidative stress and endothelial dysfunction. Chronic BMP4 infusion in C57Bl/6 and apolipoprotein-null mice also impairs endothelium-dependent vasodilation and induces arterial hypertension in an NAD(P)H oxidase–dependent manner. BMP2 and BMP4 also elicit endothelial activation, thus enhancing monocyte adhesiveness. Evidence indicates that in endothelial cells BMP2 and BMP4 activate mitogen-activated protein kinase pathways and nuclear factor-κB, at least in part, via NAD(P)H oxidase–dependent pathways. Future studies will elucidate in detail the role of BMP receptor subtypes and the interaction between downstream signaling mechanisms induced by BMP2/4 that mediate their proinflammatory effects in the cardiovascular system.

Hemodynamic Forces Regulate Vascular Expression of BMP2/4 and BMP Antagonists

Our understanding of the factors that regulate vascular BMP2/4 expression also suggests a proatherogenic pathophysiological role for BMPs. It has been established that vascular inflammation and atherosclerosis develop in hemodynamically well-defined regions. During normal vascular homeostasis, laminar shear stress maintains an antiinflammatory, antiatherogenic phenotype of endothelial cells. In contrast, adverse changes in the hemodynamic environment, particularly a combination of low shear stress and increased wall tension (eg, resulting from high pressure), elicit proinflammatory phenotypic changes favoring atherogenesis. It is significant that expression of BMP2/4 is regulated by hemodynamic forces (Figure, C). In a series of elegant studies, Jo’s laboratory has demonstrated that expression of BMP4 in cultured endothelial cells is suppressed by initiation of laminar flow. We have recently shown that laminar shear stress regulates BMP4 (but not BMP2) expression both in cultured arteries in vitro and in animal models of increased shear stress in vivo. The transcriptional mechanisms by which shear stress regulates BMP4 expression are not completely understood and may include the cAMP/PKA pathway and mitogen-activated protein kinase signaling. In contrast to atheroprotective laminar shear stress, proatherogenic oscillatory shear stress upregulates BMP4 in endothelial cells. Previous studies have demonstrated that autocrine effects of BMP4 are responsible for the increased adhesiveness of activated monocytes to endothelial cells exposed to oscillatory shear stress. Expression of BMP2 is unaltered by shear stress but can be upregulated by cellular stretch in arteries exposed to high pressure. In coronary arterial endothelial cells, expression of BMP2 also is upregulated by proinflammatory stimuli such as tumor necrosis factor-α. Surprisingly, BMP4 does not seem to be readily induced by these stimuli. BMPs are produced from inactive precursors that are proteolytically cleaved. Then, the active ligand is secreted into the extracellular space. Binding of BMPs to their cognate receptors leads to phosphorylation of Smad proteins and activation of non–Smad-dependent intracellular signal-transducing pathways (eg, ERK1/2). Smad proteins form hetero-oligomers, translocate to the nucleus, and modulate transcription of target genes. Abundant data show that the BMP signal transduction cascade can be modulated at every field of study.
A, BMP4 elicits endothelial dysfunction by activating NAD(P)H oxidase in mouse carotid arteries. Arterial segments were maintained in vessel culture (for 24 hours) in the absence and presence of recombinant BMP4 (0.1, 1, 4, or 10 ng/mL) as described.3 Arterial ring preparations were contracted by phenylephrine (10^-6 mol/L), and relaxations to acetylcholine were obtained in the absence and presence of the NAD(P)H oxidase apocynin (APO; 3×10^-4 mol/L; 30 minutes of preincubation). Data are mean±SEM (n=4 to 6 for each group). B, Scheme depicting the regulation of vascular BMP2/4 expression by hemodynamic forces. BMP2/4 elicits endothelial activation, vascular oxidative stress, and endothelial dysfunction, promoting the development of atherosclerosis and hypertension. The endothermal expression of BMP antagonists demonstrated by Chang et al likely represents a key mechanism by which autocrine/paracrine effects of BMP2/4 are modulated in the vascular wall. The regulation of BMP antagonists by shear stress and BMP4 itself suggests the existence of a negative feedback regulatory loop. Further studies evidently are needed to elucidate the role of other hemodynamic forces in controlling the expression of BMP antagonists (eg, high intraluminal pressure, increased wall tension, and/or increased pulse pressure). Chang et al convincingly showed that the expression pattern for BMP antagonists). Studies using various in vivo models of altered shear stress (eg, arteriovenous fistula models) also would provide additional information about the in vivo coordinated regulation of BMPs and BMP antagonists. It will be of great interest to determine whether these new findings apply to other vascular beds.
can play a role in microvascular remodeling. Chang et al reported that in human coronary arteries, endothelial expression of BMP antagonists (similar to that of BMP4) positively correlated with the severity of atherosclerosis. Although it is tempting to speculate that upregulation of BMP4 and BMP antagonists during plaque development is due to the disturbed flow conditions in the diseased vascular segments, one cannot exclude the possibility that other atherogenic factors (e.g., inflammatory stimuli, altered arachidonic acid metabolism) may play a role in this phenomenon. Finally, studies like those of Chang et al are extremely important because they identify novel pathways that could be targeted to attenuate vascular inflammation during the early phases of atherogenesis.

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References

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