Bone Morphogenetic Proteins in Vascular Calcification

Keith A. Hruska, Suresh Mathew, Georges Saab

Abstract—Vascular calcification is a common problem among the elderly and those with chronic kidney disease (CKD) and diabetes. The process of tunica media vascular calcification in CKD appears to involve a phenotypic change in the vascular smooth muscle cell (VSMC) resulting in cell-mediated mineralization of the extracellular matrix. The bone morphogenetic proteins (BMPs) are important regulators in orthotopic bone formation, and their localization at sites of vascular calcification raises the question of their role. In this review, we will discuss the actions of the BMPs in vascular calcification. Although the role of BMP-2 in vascular calcification is not proven, it has been the most studied member of the BMP family in this disease process. The role of BMP-2 may be through inducing osteoblastic differentiation of VSMCs through induction of MSX-2, or by inducing apoptosis of VSMCs, a process thought critical in the initiation of vascular calcification. Additionally, BMP-2 may be related to loss of regulation of the matrix Gla protein. A second BMP, BMP-7, less studied than BMP-2 may have opposing actions in vascular calcification. In postnatal life, BMP-7 is expressed primarily in the kidney, and expression is diminished by renal injury. BMP-7 is an important regulator of skeletal remodeling and the VSMC phenotype. BMP-7 restores skeletal anabolic balance in animal models of CKD with disordered skeletal modeling, also reducing serum phosphate in the process. BMP-7 also reverses vascular calcification in CKD, and reduction in vascular calcification is due, in part, to reduced serum phosphate, an important inducer of VSMC-mediated vascular mineralization and in part to direct actions on the VSMC.

Key Words: bone morphogenetic proteins | vascular calcification | chronic kidney disease | vascular smooth muscle cells | Smad6 | MSX-2

Vascular calcification may be associated with significant morbidity and mortality. Four types of vascular calcification have been identified with at least some distinct properties: intimal atherosclerotic plaque calcification, tunica media calcification, cardiac valve calcification, and vascular calciphylaxis. Tunica media calcification, also referred to as Mönckeberg’s sclerosis, is associated with aging, diabetes, and chronic kidney disease (CKD). The pathways toward calcification may differ between the types of vascular calcification, but examination of calcified vessels has revealed

Original received November 29, 2004; revision received January 24, 2005; resubmission received May 10, 2005; revised resubmission received June 17, 2005; accepted June 21, 2005.
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Circulation Research is available at http://circres.ahajournals.org DOI: 10.1161/10.1161/01.RES.0000175571.53833.6c

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many similarities between intimal and tunica media calcification. Recently, examination of calcified vessels in humans and animals revealed the expression of the osteoblast transcription factors Runx2/Cbfa1, Osterix, and MSX2, as well as chondrocyte transcription factors such as Sox9. Moreover, these calcified vessels also expressed bone matrix protein indicators of osteogenesis and chondrogenesis. Animal models and human disease demonstrate that expression of these transcription factors is essential for normal bone formation. These findings have led to speculation that vascular calcification is regulated, in part, by a process similar to bone formation. In other words, vascular calcification appears to involve cells that have developed an osteoblast-like phenotype with the ability to mineralize a specialized extracellular matrix. There are 2 types of bone formation: endochondral bone formation that involves chondrogenesis and a cartilage intermediate, and intramembranous bone formation that derives from direct differentiation of mesenchymal stem cells into bone forming osteoblasts. Intimal atherosclerotic plaque calcification involves endochondral ossification, whereas tunica media calcification is a process more akin to intramembranous bone formation.

The origin of the osteoblast-like cells in vascular calcification is controversial. One possibility would be from the vessel wall itself. Indeed, certain subpopulations of cells cultured from bovine and human aortic media have been found to spontaneously calcify. These cells have been termed calcifying vascular cells or CVCs. These same cells have subsequently been shown to have the potential for multiple mesenchymal cell lineages, including osteoblasts. Others have described circulating mesenchymal precursor cells, including certain subpopulations of CD14+ monocytes that have a similar potential. Other investigators (see reference 10 for review) have suggested that migration of adventitial pericytes or myofibroblasts into the vessel wall accounts for the mineralizing cell population in the medial artery calcification of diabetes. Although the search for the origin of the mineralizing cell goes on, it is also imperative to understand the stimulus that drives it. One possible stimulus is the bone morphogenetic proteins (BMPs), which along with the Wnt family, a disarmingly simple system are critical players in the mammalian endocrine reproductive axis.

The Bone Morphogenetic Proteins

The BMPs are a group of at least 30 proteins named for their osteoinductive properties that have important developmental roles in organogenesis in a variety of tissues. BMPs are part of the TGF-β superfamily and act by binding to a heterodimeric complex of transmembrane receptors (BMP receptor I and II) that trimerize before signaling. Binding of a BMP to its specific type II receptor results in activation of type I receptors. Signaling results from gene transcription stimulated through phosphorylation and nuclear translocation of regulatory Smad transcription factors.

The BMPs form the largest group of proteins within the TGF-β superfamily. The BMPs are known for remarkable roles as instructive signals during embryogenesis and in the maintenance and repair of bone and other tissues in the adult. TGF-β, Nodal, and related factors form a separate, structurally more divergent group in the family, also with important roles in embryogenesis. The factors in the Nodal group account for the Activin-like signals that play roles in laying out the body plan and are complimentary to the function of the BMPs in embryogenesis. The various forms of TGF-β and Activin are structurally further removed from the BMPs and are best known for their roles in late stages of embryogenesis and in the mature organism. The TGF-β are critical inhibitors of epithelial growth and immune and hematopoietic functions as well as strong promoters of connective tissue growth among many other functions. The Activins are important players in the mammalian endocrine reproductive axis.

For all of the diversity and physiological importance of responses to the TGF-β family, a disarming simple system lies at the core of signal transduction pathways. The basic signal mechanisms consist of 2 receptor serine/threonine protein kinases (receptor types 1 and 2) and a family of receptor substrates (the Smad proteins) that move into the nucleus and ActR and ActR-IIB. Ligand binding of the type 2 receptor results in activation of receptor I and II) that trimerize before signaling. Binding of a BMP to its specific type II receptor results in activation of type I receptors. Signaling results from gene transcription stimulated through phosphorylation and nuclear translocation of regulatory Smad transcription factors.
intrinsic transactivating activity, and the previously known transcription factors, AP-1, TFE3, and AML, that function independently of Smads in other contexts.\textsuperscript{25,28–32} Once a Smad complex binds the DNA, it may control the transcription of target genes by altering nucleosome structure, thereby remodeling the chromatin template. Via the MH2 domain, Smads combine the coactivators, p300-CBP, which have histone acetyltransferase activity and the corepressors TGIF, c-Ski, and SnoN, which recruit histone deacetylases.\textsuperscript{26} Thus, beyond the Smads, the signaling processes branch out toward different outcomes through the agency of specific DNA binding cofactors, coactivators, and corepressors. Differences in the kinetics and mode of interaction of the different ligands with receptors, the different receptors with Smads, and the different Smads with target genes establish functionally important—if biochemically discrete—distinctions between the various components of the basic TGF-\(\beta\) signaling mechanism. The activity of TGF-\(\beta\) factors is modulated by various families of diffusible ligand binding proteins that prevent ligand access to signaling receptors.\textsuperscript{25,26} noggin and Cordin are structurally unrelated to the differential screening-selected gene aberrative in neuroblastoma (DAN) family members, but all 3 groups act as BMP antagonists.\textsuperscript{33,34} The DAN family consists of Cer1, Cereberus, Caronte, Drn/Gremlin, PRDC, DAN, Dante, and CeCan1.\textsuperscript{35–40} These proteins may contribute to the formation of morphogen gradients during embryogenesis, to the relay of signals by extracellular signal transduction pathways, and to the homeostasis of signaling inputs in a tissue.

In addition to the regulatory Smads and coSmads which carry signals from receptors to the nucleus, a third group of Smads act antagonistically, abrogating TGF-\(\beta\) family signal transduction. The antagonistic Smads include Smad6 and Smad7. The antagonistic Smads are known to mediate negative feedback within TGF-\(\beta\) signaling pathways. Smad7 inhibits Smad phosphorylation by occupying type 1 receptors for TGF-\(\beta\), Activin, and BMP.\textsuperscript{41,42} Smad7 preferentially inhibits TGF-\(\beta\) signaling over BMP signaling.\textsuperscript{43,44} Smad7 resides predominantly in the nucleus at basal state and translocates to the cytoplasm on TGF-\(\beta\) stimulation.\textsuperscript{45} Smad6 preferentially inhibits BMP signaling by a mechanism related to competition with Smad4 for

![Figure 1. Putative BMP signaling mechanisms as related to vascular calcification. Adapted from Massagüé J and Wotton D, the EMBO J. 2000;19:1745–1754.](image-url)
binding to receptor activated Smad1 yielding inactive Smad1–Smad6 complexes. Smad6 defective mice have multiple defects in the development and homeostasis of the cardiovascular system. The ossification of the aorta in these animals in particular is suggestive of an excess of BMP signaling activity.

**BMPs in Skeletal Development and Osteoblast Regulation**

The BMPs constitute a large multigene family whose members are related to each other by relative degrees of sequence similarity, but that possess a wide ranging number of biological functions (see reference 47 for review). Family members show an identifying pattern of 7 conserved cysteine residues in the mature carboxy-terminal portion of the protein. Secreted BMP action may also be determined by the presence of extracellular antagonists with some degree of specificity. The BMPs with greatest osteogenic capacity are BMP-2, -4, -5, -6, -7, and -9. Of these, BMP-2 and BMP-4 are closely related, and BMP-5, -6, and -7 are closely related and not too distant from BMP-2 and -4. All of these BMPs except BMP-7 have been localized in sites of vascular calcification. BMP-2 and -4 have been most frequently associated with calcific arteriopathy, and BMP-7 may be, surprisingly, inhibitory (see below).

BMP-2 and BMP-7 are the best studied of the BMPs in regard to possible roles in vascular calcification. Both have significant importance in bone development and the development of a wide array of tissues outside of bone. Mice genetically engineered to be deficient in BMP-2 die between days 7 and 10 of gestation of cardiac defects before bone formation. In bone formation, BMP-2 and BMP-7 act by inducing the expression of the critical transcription factors Runx2 and Osterix in mesenchymal stem cells, thereby committing them and directing them in osteoblast differentiation. Mice genetically engineered to be deficient in BMP-7 die postnatally with skeletal patterning defects and hypomineralization involving the ribcage, skull, and hind legs along with renal dysplasia and ocular defects. The limited tissue defects in these mice likely occur as a result of overlapping expression of other BMPs, particularly BMP-2, -4, -5, and -6.

The absence of normal kidney development suggests that BMP-7 is crucial in the process of nephrogenesis. Indeed, expression of BMP-7 is first detected in the ureteric bud and later in the condensing mesenchyme in the developing kidney. Loss of BMP-7 expression inhibits the induction of the condensing mesenchyme and tubulogenesis. In postnatal life, expression of BMP-7 is also largely in the kidney with the glomerular podocytes and distal nephron derivatives of the ureteric bud having high levels of expression compared with the rest of the body. Furthermore, in animal models of renal injury, expression of BMP-7 is variable and in most injuries the message levels measured by in situ hybridization are reduced. Because renal injury directly impairs skeletal anabolism, the mechanism of this kidney–bone connection requires definition as to the relationship to BMP-7.

Although both BMP-2 and BMP-7 have osteoinductive properties, studies have been somewhat inconsistent in regard to their relative potencies. Fetal rat calvarial cell (FRCC) cultures have a variety of osteogenic cells in various stages of differentiation. Flow cytometric analysis has revealed that although treatment of committed osteoblast precursors with BMP-7 enhanced bone nodule formation, treatment actually inhibited it in uncommitted cells. Furthermore, treatment with BMP-7 among uncommitted cells resulted in chondrocyte and adipocyte differentiation. Similarly, others have shown BMP-2 treatment of C3H10T1/2 pluripotent mesenchymal stem cells resulted in a markedly higher increase in alkaline phosphatase activity, a marker of early osteoblast differentiation, as compared with BMP-7, which had minimal effect. However, other studies have shown that BMP-7 is able to induce osteogenesis in a time- and dose-dependent manner in C3H10T1/2 cells. Treatment of these cells with BMP-7 initially results in chondrogenesis and is later followed by osteogenesis. It is possible that BMP-7–induced osteogenesis may occur indirectly as a result of chondrogenesis in this cell line. Indeed, coculture of C3H10T1/2 cells with chondrocytes results solely in osteogenesis. Despite these findings, we have recently shown that BMP-7 was potent and sufficient as a sole factor in directing human marrow mesenchymal stromal cells toward an osteogenic lineage (induction of Cbfal) and stimulating differentiation (induction of osterix) to the osteoblast (induction of mineralization and osteocalcin). Thus, despite potential similarities in signaling and receptor activation, there is clear evidence of major differences in the actions of BMP-2 and BMP-7 in mineralizing tissues.

**The Bone Morphogenetic Proteins in the Vasculature**

Vascular smooth muscle cells (VSMCs) normally reside in the vessel wall media in a differentiated state wherein their contractile properties regulate vascular tone. However, VSMC phenotype is characterized by the ability to reversibly enter a synthetic state of proliferation and production of large amounts of extracellular matrix. Transition into the synthetic state is associated with a loss of smooth muscle cell (SMC) markers associated with contractility. Experimentally, this phenomenon can be induced with various growth factors and serum stimulation in vitro. This transition is thought to play a role in the pathogenesis of atherosclerosis and Mönckeberg sclerosis because both are associated with decreased expression of SMC markers in plaques and areas of calcification. Much like the expression of osteoblast transcription factors, the expression of BMPs have been described in atherosclerotic plaques, BMP-2, BMP-4, and BMP-6 have been localized to areas of vascular calcification. Subsequently, studies were performed to evaluate what effects the BMPs had in this phenotypic transition.

BMP-2 has been shown to inhibit VSMC proliferation when stimulated with serum or growth factors in vitro. Inhibition of proliferation may in part be caused by p21 inhibition of cyclin dependent kinases and subsequent cell cycle arrest. Furthermore, adenovirus-mediated transfer of the BMP-2 gene reduced intimal hyperplasia induced by balloon injury. However, BMP-2 surprisingly decreases the expression of SMC markers in vitro after growth arrest is...
Proposed Role of BMP2/MSX2 in Vascular Calcification

BMP-2 induces VSMC proliferation, and BMP-2 induction in the vasculature may be related to oxidative stress, inflammation, and hyperglycemia. BMP-2 is a powerful bone morphogen and its expression may entrain the elaboration of osteogenic transcriptional regulatory programs in the arterial tree. BMP-2 induces both Msx-2 and Runx/Cbfal in VSMCs (Figure 2). Msx-2 is required for intramembranous bone formation, and Cbfal is critical in osteoblast differentiation, endochondral bone formation, and neovascularization. Recent studies demonstrate that Msx-2–dependent transcriptional programming may drive osteoblastic lineage development.

MSX2 appears to be a critical gene in vascular calcification upregulated by the action of BMP-2. MSX2 is a member of the homeobox gene family and plays an important role in bone formation and temporal spatial timing of osteoblast differentiation. A gain-of-function mutation in the MSX2 homeodomain causes the autosomal dominant Boston-type craniosynostosis. The effect of the gain function mutation in MSX2 promotes enhanced DNA binding to promoter elements of genes associated with mineralization. MSX2 deficiency produces defective skull ossification and persistent calvarial foramen. Haploinsufficiency of MSX2 causes persistent patency of the parietal foramen. The skull and the clavicles are bones formed by intramembranous mineralization, a process without a cartilage intermediate as compared with endochondral ossification. Thus, MSX2 is a critical regulator of intramembranous bone formation. The mineralization process of tunica media calcification is akin to intramembranous bone formation, and studies demonstrate MSX2 expression and function in vascular media calcification.

Induction of Vascular Matrix Mineralization by BMP-2

BMP-2 is expressed by cells in atherosclerotic lesions and in periadventitial myofibroblasts and tunica media cells. BMP-2 induction in the vasculature may be related to oxidative stress, inflammation, and hyperglycemia. BMP-2 is a powerful bone morphogen and its expression may entrain the elaboration of osteogenic transcriptional regulatory programs in the arterial tree. BMP-2 induces both Msx-2 and Runx/Cbfal in VSMCs (Figure 2). Msx-2 is required for intramembranous bone formation, and Cbfal is critical in osteoblast differentiation, endochondral bone formation, and neovascularization. Recent studies demonstrate that Msx-2–dependent transcriptional programming may drive osteoblastic lineage development.

Figure 2. Proposed role of BMP2/MSX2 in vascular calcification. Depending on the setting, BMP2 can stimulate an intramembranous-like ossification program or an endochondral-like program, the difference being whether or not SOX9 is activated.
The effect of MSX2 is through upregulation of osterix (Osx), a global transcriptional regulator of mineralization and osteoblast differentiation. Osterix is a recently discovered zinc finger–containing transcription factor that is expressed in all developing bones that is regulated by both RUNX2/Cbfa1 and MSX2. Osterix activity is required for induction of alkaline phosphatase and mineralization by the RUNX2/Cbfa1 pathway, and it is a second osteoblast specific transcription factor activated by BMP2 downstream of RUNX2/Cbfa1. Osterix deficiency produces the absence of bone formation. In endochondral skeletal elements of osterix-null mice, mesenchymal cells together with osteoclast and blood vessels invade demineralized cartilage matrix. However, there is no deposition of bone matrix and the absence of mineralization. Similarly, cells in the periosteum and the condensed mesenchyme of membranous skeletal elements (the skull and the clavicle) cannot differentiate into osteoblasts. These cells do, however, express Runx2/Cbfa1, another transcription factor required for bone formation. In contrast, osterix is not expressed in Runx2/Cbfa1-null mice. Thus osterix acts downstream of Runx/Cbfa1. In vascular calcification of the tunica media type osterix is downstream of MSX2 and RUNX2/XCbfa1, and its activation is most likely the cause of the osteoblast phenotype and matrix mineralization.

The role of BMP-2 in vascular calcification may be modulated by the effects of the matrix Gla protein (MGP), an inhibitor of calcification. Mice genetically engineered to be deficient in MGP develop extensive medial calcification in the absence of atherosclerosis. Furthermore, VSMCs derived from the aortas of MGP-deficient mice undergo chondrogenic and osteogenic differentiation when treated with BMP-2, whereas control VSMCs do not. In atherosclerosis and Mönckeberg sclerosis, the expression of MGP is globally decreased before calcification. Because BMP-2 has only been described in calcified vessels, vascular calcification may occur via unopposed BMP-2 action, partially secondary to loss of MGP expression. Similar results occur with the disruption of the BMP inhibitor Smad 6 gene. Targeted mutation of Smad 6 by insertion of a LacZ reporter into the coding region (exon 2) of the gene demonstrated that the expression of Smad 6 was limited to the heart and vasculature. Furthermore, interference with Smad 6 function produced aortic ossification and hypertension in adult mice. Vascular calcification only occurred in areas where Smad 6 was normally expressed, further suggesting that unopposed action of a TGF superfamily member including the BMPs may have led to vascular calcification. In addition, the calcification associated with Smad 6 and MGP deficiency was associated with a cartilaginous metaplasia, suggesting that unopposed BMP action may induce a phenotypic change in VSMCs.

**Effect of BMP-7 on VSMC Phenotype**

BMP-7, in contrast to BMP-2, has been shown to promote the VSMC phenotype. This is because of induction of p21 as well as upregulation of inhibitory Smads 6 and 7. The actions of BMP-7 on VSMCs in vitro are in agreement with in vivo studies discussed above demonstrating a role of inhibitory Smads in the homeostasis of the adult cardiovascular system. A difficult issue is how two closely related proteins, BMP-2 and BMP-7, which use the same or similar receptors and activate the same regulatory Smads could have such different effects in VSMCs. There are multiple mechanisms for this phenomenon in VSMC that remain to be discovered. These include specific receptor mechanisms such as endoglin (a Type III TGFβ receptor), which binds BMP-2 and not BMP-7. Another is the new concept of BMPR coreceptors that may be specific for one or the other BMP. Another possibility is a receptor quaternary complex sensitive to only one or the other BMP. Finally, BMP specific Smad independent signaling may be the basis for differential actions of the BMPs. All of these possibilities are being analyzed to explain differential signaling in the VSMC.

**The Bone Morphogenetic Proteins: A Link between Bone Formation, Phosphate, and Vascular Calcification**

In CKD, wherein calcification of the tunica media is very prevalent, a skeletal remodeling defect is uniformly observed referred to as renal osteodystrophy (see reference 97a for review). The remodeling defect type is dependent on the adaptation to the loss of skeletal anabolism produced by kidney disease, ranging from an adynamic bone disorder (absence of adaptation) to high turnover osteodystrophy produced by secondary hyperparathyroidism (presence of adaptation). In high turnover osteodystrophy bone resorption exceeds bone formation even though the latter is also increased, and phosphorus is delivered to the blood stream as a result of the excess bone resorption. In low turnover osteodystrophy, phosphorus is prevented from leaving the blood stream into the skeleton by the decrease in bone formation rates leading to frequent hyperphosphatemia. A net effect of CKD, as a result of renal osteodystrophy, is a hyperphosphatemic stimulus to the vasculature.

We have examined the effects of CKD on vascular calcification in mice genetically engineered deficient in the low-density lipoprotein receptor (LDLR −/−) and fed a high-fat diet. These mice develop diabetes, obesity, significant atherosclerosis, and vascular calcification. We surgically induced CKD in these mice and examined the effects on vascular calcification. LDLR −/− high fat–fed mice with CKD exhibited more extensive vascular calcification in both the intima and the tunica media than those without CKD. Subsequently, we have shown that high-fat feeding in LDLR −/− mice without CKD results in an increase in serum phosphorous compared with chow feeding and that CKD worsens the hyperphosphatemia. There were no dietary differences in phosphorous content to account for these differences. Elevated phosphorous may provide the link between vascular calcification and the LDLR −/− high-fat fed mouse. Indeed, in vitro studies have shown that phosphorous, as phosphate, induces VSMCs to calcify and undergo osteogenic differentiation. This phenotypic change induced by phosphate appears to involve a sodium-phosphate cotransporter (Pit-1). It is not known whether phosphate induces BMP-2 expression in calcifying VSMCs.
Elevations in serum phosphorous in the LDLR −/− high fat–fed mouse with or without CKD likely occur as a result of changes in skeletal remodeling. Indeed, we have shown that high fat feeding significantly reduces bone formation, a process that is worsened with CKD (despite the development of secondary hyperparathyroidism). In other words, the LDLR −/− high fat–fed mice with CKD have the adynamic bone disorder.

Furthermore, treatment of LDLR −/− high fat–fed CKD mice with BMP-7 restores skeletal remodeling to normal, reversing hyperphosphatemia without a change in renal excretion of phosphorous, and prevents or even reverses vascular calcification. Direct reduction of the serum phosphate using phosphate binder therapy also partially reduced vascular calcification but not as effectively as BMP-7. Thus, BMP-7 may help prevent vascular calcification through increased skeletal deposition (Figure 3). Indeed, we have also shown that there was a significant inverse correlation between bone mineralization rates and the extent of aortic calcification in this model.

The association between vascular calcification and the adynamic bone disorder in CKD is an emerging topic. As stated before, the adynamic bone disorder is associated with an increased mortality as compared with other types of renal osteodystrophy. Furthermore, a recent study has shown a significant correlation between the adynamic bone disease and vascular calcification. This may in part be caused by an inability of bone to “buffer” dietary calcium and phosphorus loads. Indeed, calcium has recently been shown to increase Pit-1 mRNA in VSMCs in vitro. Thus, transient elevations in serum calcium may sensitize VSMCs to phosphorous. We hypothesize that adynamic bone may similarly be unable to buffer serum phosphorous, further promoting vascular calcification. Thus BMP-7 may help prevent vascular calcification through upregulation of the VSMC contractile phenotype, inhibitory Smads, and, in the case of CKD and the adynamic bone disease, an increase ability to buffer serum phosphorous (and calcium) by the skeleton (Figure 3).

Conclusion

The bone morphogenetic proteins (BMPs), along with the Wnt family of glycoproteins, are the most important anabolic factors in bone formation. Because vascular calcification in CKD appears to be regulated in a process similar to bone formation, it is intuitive to consider the BMPs in the pathogenesis of vascular calcification. However, although the roles of the BMPs in osteogenesis are well documented, their roles in vascular calcification are more complex and less defined. Indeed, whereas BMP-2 is a strong basic causative factor in vascular calcification, another BMP, BMP-7, appears to inhibit it. Further studies defining the precise role of BMPs in vascular calcification are needed, particularly with regards to how factors with similar signaling cascades can have such divergent effects.

Acknowledgments

The work was supported by NIH Grants DK059602, DK09976 and AR41677 to Keith A. Hruska and a grant from Johnson and Johnson. The authors wish to thank previous renal fellows, Matthew Davies and Richard Lund, for their contributions to the work cited here. Also, thanks to Helen Odle for her work on the manuscript and to Francis Farrell and Kuber Sampath for valuable discussion.

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Circ Res. 2005;97:105-114
doi: 10.1161/01.RES.00000175571.53833.6c

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