Osteopontin: an emerging therapeutic target in uraemic vascular disease

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The incidence of cardiovascular disease remains high in the population with renal failure and constitutes the leading cause of morbidity and mortality in these patients. According to the U.S. Renal Data System 2011 Annual Data Report, the rate of death among dialysis patients attributable to cardiovascular disease was 40% and 5% to acute myocardial infarction.¹ However, the mechanisms by which renal failure accelerates development of vascular disease and magnifies cardiovascular morbidity and mortality remain elusive.

As a common component in development of atherosclerosis, calcification characterizes vascularopathy, contributes to plaque rupture and thrombosis, and predicts high mortality in hemodialysis patients.² In addition to traditional risk factors, this complication is associated with non-traditional factors such as elevated serum phosphorus and serum calcium × phosphate product in uraemia.³ However, recent evidence suggests that the mechanism underpinning vascular calcification in uraemia is more than passive metastatic calcification, but an active cell-mediated process. Furthermore, osteopontin (OPN) has emerged as a key regulator in development of atherosclerosis-associated vascularopathy.

OPN, a small integrin-binding ligand, N-linked (SIBLING) glycoprotein first identified in 1986 as a bone matrix protein in osteoblasts, is expressed in various immune and vascular cells and secreted in body fluids to carry multi-domain functions. Its expression in the healthy heart and blood vessels is very low, but consistently up-regulated following injury, and predicts poor cardiac function.⁴ In the normal human kidney, distal tubular cells manifest constitutive OPN expression that increases in glomerulonephritis. Uraemic patients have increased levels of OPN not only in the plasma, correlating with coronary calcification,⁵ but also in smooth muscle cells (SMCs) in the aorta,⁶ and macrophages surrounding atheromatous plaques were identified as the OPN production and excretion of OPN is possibly elaborately and adjusted on different stages, so that interaction of various factors and markers may affect its action.⁷

Furthermore, OPN deficiency has been shown to inhibit formation of atherosclerotic and inflammatory lesions in ApoE⁻/⁻ mice,¹⁰ whereas OPN transgenic mice fed a high-cholesterol diet exhibit accelerated fatty-streak lesion formation.¹¹ However, whether OPN contributes to uraemic atherogenesis remains obscure.

In this issue, Pedersen et al.¹² demonstrates a notable role of OPN in development and progression of plaque in uraemia achieved by five of six nephrectomy in an OPN⁻/⁻/ApoE⁻/⁻ mice model. The surface area of a nephrectomy-induced plaque in the aortic arch was associated with elevations of OPN systemic levels and mRNA expression in the aorta, and positively correlated with plasma OPN levels. Notably, OPN deficiency blunted aortic plaque progression and lipid content in uraemic mice, and also lowered monocyte chemoattractant protein-1 and interleukin-6 mRNA expression in bone marrow-derived macrophages and foam cells in response to a pro-inflammatory stimulus. These observations represent an extension of their previous finding that OPN was the most significantly up-regulated gene in uraemia, accompanied with vacuolization and necrosis of SMC within the media layer.¹³ The present work reinforces the causal link between OPN and SMC de-differentiation, a key process in atherogenesis, because OPN prevented uraemia-induced down-regulation of the transcription factor myocardin and of alpha-smooth muscle actin, indicators of a switch from contractile to synthetic phenotype. Therefore, these findings suggest that both systemic and local OPN may facilitate formation and progression of atherosclerotic plaques under uraemic conditions. Yet, it would have been useful if the status of phosphate and calcium × phosphate product were also reported.

However, in this study transplantation of bone marrow (BMT) from OPN⁻/⁻ into uraemic mice did not prevent either formation of the atherosclerotic plaque in the aorta or SMC de-differentiation. Given that systemic OPN levels remained elevated in transplanted uraemic mice, production and excretion of OPN is possibly elaborately and adjusted by multiple factors, so that BMT may not completely deplete its production by other recipient cells. In addition, it is not clear whether OPN regulates atherogenesis remotely or indirectly, as its expression was markedly lowered in the aorta of uraemic mice following BMT. On the other hand, OPN could exert pleiotropic effects at different stages and under different conditions, so that interaction of various factors and modulators may affect its action.¹⁴
In summary, current studies suggest that inhibition of excessive OPN is likely to confer protection in both cardiovascular and end-stage renal diseases, as shown in Figure 1. Activated angiotensin-II and transforming growth-factor-β also favour modulation of OPN in regulation of vascular complications. Nevertheless, one must recognize that uremic vascular disease involves alterations in a broad spectrum of proteins and biomarkers in response to deceased renal function. The tight interaction among these factors not only contributes to the challenge of defining the precise mechanisms of OPN, but also importantly underscores the necessity for homoeostasis. In addition to careful adjustment of phosphate levels, whether modulation of OPN would affect haematopoietic stem cell proliferation or immune responses to infections that complicate uraemia need to be identified. The potential effect of OPN inhibition or depletion on cardiac function is yet unexplored. The upstream modulators during cardiovascular and kidney disease need to be identified. Future work will expand on this exciting progress in our understanding of OPN and its multi-domain physiological roles to halt, ameliorate, or reverse, vascular calcification and plaque formation in patients with uraemia.

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**References**


