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Short Commentary Open Access

Osteopontin in Vascular Calcification: A Central Player or Accidental Witness?

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Abstract

Osteopontin (OPN) is an integrin-binding ligand belonged to the family of N-linked glycoprotein, which is produced by activated mononuclears and linking systemic inflammation, atherosclerosis, and vascular remodeling. There is a large body of evidence regarding the controversial role of OPN in vascular calcification, while OPN is considered a pretty accurate biomarker of vascular remodeling with promising predictive value for cardiovascular (CV) disease and CV events. The short communication depicts the discussion about some controversies regarding exclusive role of OPN in several phases of vascular remodeling.

Keywords: Hypertension; Vascular remodeling; Inflammation; Calcification; Osteopontin; Regulation

Osteopontin in Vascular Calcification

Recent preclinical and clinical studies have shown that vascular calcification is inexorable pathological process leading to mechanical rigidity and stiffness of vascular wall, endothelial dysfunction, development and accelerating atherosclerosis even in the absence of established cardiovascular (CV) disease [1-3]. Ectopic calcification is represented by several mutually counteracting molecular mechanisms, i.e., oxidative stress, microvascular inflammation, immune cell-to-cell cooperation, accumulation of lipids and extracellular proteins, vascular reparative systems, and metabolic disorders [4-6]. All these processes are under tight regulation of vitamin D, parathyroid hormone-related peptides (fibroblast growth factor, transcription factor Sox2, beta-catenin, etc.) and matricellular proteins such as osteopontin (OPN) and phosphate [7-10].

OPN is an integrin-binding ligand belonged to the family of N-linked glycoprotein, which is produced by activated mononuclears and linking systemic inflammation, atherosclerosis, and vascular remodeling via regulating ectopic calcification and extracellular matrix accumulation [11]. Indeed, OPN corresponded to hyperphosphatemia, conventional and nonconventional CV risk factors and CV disease mortality [10]. It has been postulated that OPN appeared to block vascular calcification most likely by preventing calcium phosphate crystal growth and inducing cellular mineral resorption. However, the role of OPN in vascular calcification is pretty controversial. The first controversy is based on opinion regarding that the OPN was found in elevated concentration in patients with established vascular calcification, atherosclerosis, and CV disease associated with severe vascular remodeling including hypertension, chronic kidney disease, diabetes mellitus [4,9,12]. In this context, OPN is an accurate biomarker of vascular remodeling closely relating to inflammation intensity, glucose level and pro-thrombotic state with promising predictive value for CV events [13].

However, there is large body of evidence that OPN could be an inducible inhibitor of vascular calcification *in vivo* and that the elevation of OPN level in serum reflects an involvement of protective mechanisms against ectopic calcium deposition [14]. Indeed, OPN deficiency may attenuate development and accelerating atherosclerosis increasing susceptibility to calcium deposition in smooth muscle cells [15,16].

Second controversy relates to a widely known fact regarding that the OPN is strongly induced in mononuclear and myeloid cells acting as pro-inflammatory mediator of direct and indirect vascular injury leading to endothelial dysfunction [9,17,18]. Interestingly, exogenous OPN is able to inhibit a differentiation of activated macrophages into osteoclasts in vascular wall and attenuate shaping M2-phenotype of macrophages with anti-inflammatory ability [9]. Thus, mononuclears obtained from patients with and without established vascular calcification may reply to OPN in different way that confirms being alternatively shaping mononuclears in vascular wall during ectopic calcification. Probably, OPN exerts a pivotal role in turning M1 phenotype of macrophages into M2 phenotype in vascular calcification that coordinates reducing expression of several pro-inflammatory factors and attenuating vascular osteoclast formation.

The next controversy allows us considering about a cause of interrelationship between inflammatory cytokines, overproduction of reactive oxygen species and OPN expression in individuals with established CV diseases. Inflammatory-induced OPN through NADPH oxidase signaling cascade may regulate an activation of pro-matrix metalloproteinase 9 in aortic mesenchymal cells, which play a central role in vascular reparation [19] acting as endogenous repair system together endothelial progenitor cells [6]. Moreover, deficiency of OPN presentation in aorta associated with increased risk of aneurism formation, thrombosis and fissuring plaque cap [20]. Whether OPN is a primary regulator of exaggerated inflammation cascade in the target cells via control of proliferative response or non-specific messenger, which protects vascular wall against calcium deposition through blockage of tissue metalloproteinases is not fully understood. However, there is evidence that inhibition of OPN prevented vascular calcification [21]. How similar evidence relates to clinical findings regarding predictive value of circulating OPN in individuals with and without established CV diseases is not clear [22]. Large clinical studies are required in

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future to explain in details the role of OPN as a biomarker of CV events and CV diseases and as well as a possible target of medical care.

Conclusion

OPN is considered a multi-directed factor contributing in several phases of vascular remodeling including calcium accumulation, atherosclerosis, vascular reparation and microvascular inflammation. The role of OPN as a pretty accurate biomarker of CV risk, CV diseases and CV events are actively investigated, while there are several controversies in final effects of OPN regarding vascular calcification based on multimodal pathogenetic capabilities of the molecule. Future investigations are needed to understand the possible role of OPN in biomarker-guided therapy of the CV disease and assay of vascular remodeling risk.

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