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Review Article

Matricellular Proteins as Biological Markers in Vascular Remodelling and Cardiovascular Outcomes

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Abstract

Matricellular proteins include several peptides, glycopeptides, i.e. osteopontin (OPN), osteoprotegerin (OPG), osteonectin (OSN), osteocalcin (OCN), sclerostin, and components of RANKL/RANK system. The main biological role of matricellular proteins is bone and extracellular matrix development, modeling, and remodeling and regulation of bone endocrine function. More evidences indicate that matricellular proteins are involved in calcification at ectopic sites, and they might play a pivotal role in atherosclerosis, plaque formation, vascular remodeling and integrity, neovascularization and malignancy. Matricellular proteins are intricately prone regulation by ischemia, hypoxia signaling system, hormones, electrolyte and mineral changes, inflammation, and they might involve in coupling angiogenesis and osteogenesis during bone development and repair. Although there are not sufficient evidences that the clinical correlations of circulating levels of matricellular proteins in subjects with documented cardiovascular diseases might have predictive value, it has been suggested that exaggerated level of OPG and probably OPN and OSN would confer a better prognosis in coronary artery disease patients, especially those who are underwent revascularization procedures or have acute / acutely decompensated heart failure. This review is dedicated the discussion of controversial role of the matricellular proteins among patients with cardiovascular disease and assay a predictive value of these proteins as biomarker at risk stratification.

Keywords: Matricellular proteins; Osteopontin; Osteoprotegerin; Osteonectin; Osteocalcin; Cardiovascular diseases; Age-related diseases; Metabolic comorbidities

Abbreviations

ACS: Acute Coronary Syndrome; CAD: Coronary Artery Disease; CABG: Coronary Artery Bypass Grafting; CHF: Chronic Heart Failure; CRP: C - reactive Protein; EPCs: Endothelial Progenitor Cells; MACE: Major Adverse Cardiac Events; MI: Myocardial Infarction; MMP: Matrix Metalloproteinase; OPN: Osteopontin; OPG: Osteoprotegerin; OSN: Osteonectin; OCN: Osteocalcin; RANK: Receptor Activator of Nuclear Factor-κB; RANKL: RANK Ligand; TNF: Tumor Necrosis Factor; TRAP: TNF Receptor-associated Factor

Introduction

Matricellular proteins are main components of the extracellular matrix which are highly expressed in the bone developing, vascular remodeling, and tissue regeneration [1]. Members of this protein class serve as biological mediators of cell function by interacting directly with cells or by modulating the activity of growth factors, proteases, other extracellular matrix proteins [2-4]. Within past decade substantial progress has been made in our understanding of the molecular mechanisms by which these proteins to regulate bone mineralization, vascular integrity and remodeling [5]. Matricellular proteins are multifunctional growth factors that are activated in response to a hypoxic bone micro-environment stimulates the transcription of multiple genes [6, 7]. They contribute bone development and remodeling, as well as extra bone tissue calcification, vascular integrity and remodeling, atherosclerosis and plaque formation, angiogenesis and neovascularisation [8, 9]. Moreover, matricellular proteins are intricately prone regulation by ischemia, hypoxia signaling system, hormones, electrolyte and mineral changes, inflammation, and they might involve in coupling angiogenesis and osteogenesis during bone development and repair [8]. In this review is discussed controversial role of the matricellular proteins among patients with cardiovascular disease.

Information Sources Searched

English writing original peer-reviewed papers and high quality reviews, including meta-analysis, published after 1992 and cited in data based Medline, Index Medicus, and SciVerse Scopus were screened according inclusion criteria. The inclusion criteria used in selecting the papers cited are observational/epidemiologic studies and animal/clinical investigations regarding matricellular proteins. The keywords used for searching are matricellular proteins, vascular remodeling, vascular calcification, animal and clinical studies, osteopontin, osteoprotegerin, osteonectin, osteocalcin, cardiovascular diseases. Articles that have not affordable full text and were excluded from further analysis.

Biological Role of Matricellular Proteins

It has been previously reported that the bone-related proteins include osteopontin (OPN), osteoprotegerin (OPG), osteonectin (OSN), osteocalcin (OCN), sclerostin, and RANKL/RANK system

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Table 1: The biological effects of matricelluar proteins.

Bone-related proteins	Main direct effects	Secondary direct effects	Indirect effects
OPN	Binding of specific apatite crystal faces thereby governing its function as a bone mineralization inhibitor [28]	Up-regulation of mineralization at sites of ectopic calcification, i.e. vascular wall, valvular leaflets, kidney, and gall [53, 54]	Tissue remodeling [55] Inflammation [17] Regulation of immunity [19, 20]
OPG /RANK / RANKL system	Inhibitor osteoclastogenesis [21]	Protection of the skeleton from excessive bone resorbtion and protection of tissue injury beyond bone [51, 22]	Regulation of cell metabolism and extracellular matrix modeling, mediator for innate and adaptive immunity [25, 26]
OSN	Supporting of osteoblastogenesis [27]	Regulator of fibrosis and increased extracellular matrix deposition [28]	Regulator of cell metabolism, glucose homeostasis, myoprogenitor cell differentiation [29]
OCN	Proosteoblastic effect [30, 31]	Supporting of bone-building function [32]	Regulation of glucose homeostasis, fertile function, the fat cells and male gonad endocrine activity [34, 36, 37]
Sclerostin	Negative regulator of bone growth through inhibition of osteoblastogenesis [39]	Regulation of bone modelling, remodelling, and homeostasis [34, 39]	Regulator of vascular and tissue calcification [34]

Abbreviations: OPN: Osteopontine; OPG: Osteoprotegerine; RANK: Receptor Activator of Nuclear factor-κB; RANKL: RANK Ligand; OSN: Osteonectine. OCN: Osteocalcin.

[10]. The most common of biological function of matricellular proteins is the control of bone mineralization processes [11]. Although the innate pathophysiological mechanisms of bone remodeling balance are not fully defined, matricellular proteins are considered turnover factors directly regulated bone formation and resorbtion and as well as via mediating effects of co-regulators, such as inflammatory cytokines, homocysteine, oxidized lipids, sex steroids, vitamin D, vitamin K and others [12]. Therefore, they are involved in multiple level controls for extra-bone mineralization at ectopic sites, i.e. vascular wall, valvular leaflets, kidney, gall, tendons, muscles. The matricellular proteins are expressed in wide spectrum of cells (antigen presenting cells, preosteoblasts / osteoblasts, osteocytes, chondrocytes, fibroblasts, endothelial cells, smooth muscle cells, epithelial cells), as well as skeletal muscles, mammary glands, and several organs (inner ear, brain, placenta and kidney) [13].

All matricellular proteins realize their direct (regulation of biological mineralization) and indirect (tissue remodeling and regulation immunity) biological effects (Table 1) via surface-expressed receptors that are presented as CD44 and various types of integrins (avb1, avb3, avb5, avb6, a4b1, a5b1, a8b1, a9b1) [14]. Recent investigations have been shown that bone-related proteins may play a pivotal role in atherosclerosis, cardiovascular diseases, chronic rheumatic diseases, multiple sclerosis, inflammation bowel diseases, autoimmune disorders, cancer and malignancy [15].

Osteopontin

Osteopontin (OPN, secreted phosphoprotein 1 -SPP 1, 44 kDa bone phosphoprotein, sialoprotein 1, 2ar, uropontin, and early T-lymphocyte activation-1 [Eta-1]) is a secreted low-molecular (41 – 75 kDa) matricellular protein. OPN is defined as integrin-binding ligand (N-linked glycoprotein) that is involved in several physiological and pathological processes. OPN belongs SPARC (secreted protein acidic and rich in cysteine) family and demonstrates prominent roles in cell proliferation, migration, and differentiation, apoptosis, adhesion, angiogenesis, tissue repair and regulation of extracellular matrix remodeling. There are evidences regarding the pivotal role of OPN in carcinogenesis and metastasis [16].

OPN is encoding by a single copy gene, but exists in various isoforms (OPNa, OPNb, and OPNc) as a result of alternative splicing, alternative translation and different posttranslational modifications [17]. Despite functional role of OPN isoforms in systemic inflammation is essential to understanding, over expression of OPNa, OPNb, and OPNc isoforms was not found in similar clinical settings [18]. In fact, presence of OPNc isoform associates well with diabetes mellitus and obesity [17]. The role of OPNa, OPNb, and OPNc in vascular remodeling is under recognized. OPN interacts with several integrins via two domains: Arg159-Gly-Asp161 (RGD) sequence binding to α(v) -containing integrins, and Ser162-Val-Val-Tyr-Gly-Leu-Arg168 (SLAYGLR) sequence binding to α(4) β(1) , α(4) β(7) and α(9) β(1) integrins [19]. This interaction plays a pivotal role in regulating migration, survival, and accumulation of macrophage and other types of antigen presenting cells. Indeed, OPN may induce the transcription of interleukin (IL)-6, and reduced tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and IL-10 [17]. Therefore, after translocation into nucleus OPN may interact with p85α regulatory subunit of the signaling kinase, i.e. phosphoinositol-3-kinase that leads to protection of Bcl-6 from ubiquitin-dependent proteasome degradation and inducing apoptosis [20]. Overall, OPN is considered a mediator regulated the extracellular matrix modeling and interactions between cells through growth factor signaling pathway, cell adhesion, migration, and proliferation.

Osteoprotegerin

Osteoprotegerin (OPG) is a member of the tumor necrosis factor receptor super family and is a soluble secreted protein produced by osteoblasts, osteogenic stromal stem cells and activated mononuclears [21]. OPG acts as a decoy receptor for RANKL and thus inhibits osteoclastogenesis. The main biological role of OPG is protection of the skeleton from excessive bone resorbtion and protection of tissue injury beyond bone [22]. These effects realize by binding OPG with specific ligand named RANKL that leads to prevention of interacting OPG with RANK [23]. An imbalance in the RANKL/RANK/OPG axis, with decreased OPG and/or increased RANKL, is associated with diseases that favor bone loss, including osteoporosis [24]. Therefore, recent studies showed that OPG has been identified as candidate mediators for paracrine signaling in cell metabolism and extracellular matrix regulation but have also been shown to modulate dendritic cells and activated T cells, as well as to promote B-cell maturation and antibody response, which suggests a role in both innate and adaptive immunity [25, 26].

Osteonectin

Osteonectin (OSN, BM-40) is secreted extracellular matrix

glycoprotein that belongs to SPARC family (secreted protein acidic and rich in cysteine) and expressed in active remodeling in the skeleton and other tissues [27]. The main biological effect of ONC is considered a regulator of fibrosis and increased extracellular matrix deposition [28]. Overall, OSN supports osteoblastogenesis and is prone over expression on surface of osteoblasts in response of effect of proinflammatory cytokines, sex hormones, vitamin D3, and several growth factors. Therefore, OSN together myostatin, insulin-like growth factor I, irisin and osteocalcin, may be associated with the interactions between muscle tissues and bone metabolism through the commitment of myoprogenitor cells to the osteoblast lineage [29].

Osteocalcin

Osteocalcin (OCN, bone γ-carboxyglutamic acid-containing protein, bone Gla-protein) is a small (49 amino acid residues) osteoblast-specific non-collagenous protein that is specially synthesized and secreted by osteoblast and osteocyte [30]. Synthesis of OCN is under control of is regulated by 1α, 25-dihydroxy-Vitamin D3 [31]. OCN is secreted by bone osteoblasts in response to stimulation of osteoblastic differentiation and osteocytic maturation [32]. The most of OCN is found in bone matrix and only a small amount in circulation [33]. The main biological role of OCN is proosteoblastic effect or bone-building function [34]. This effect is realizes through the appropriate OCN receptor (GPRC6A) [35]. Therefore, OCN regulate glucose homeostasis, fertile function, the fat cells and male gonad endocrine activity and be regulated by insulin and the neural system [31, 34]. There are evidences that plasma OCN is inversely related to fat mass and plasma glucose [36] and that leptin may effect on OCN carboxylation through the hypothalamus [37]. Finally, OCN is considered an effector switched dysmetabolic [38]. Notwithstanding, OCN is well known regulator of body energy metabolism, it still remained unclear as to how OCN might modulate extra bone mineralization and vascular function.

Sclerostin

Sclerostin (SOST) is low molecular signal secreted cystine-knot protein that widely expressed on surface of osteocytes and plays essential roles in bone formation, modelling, remodelling, and homeostasis [34]. SOST acts a negative regulator of bone growth through inhibiting the canonical Wnt signalling cascade by binding to and blocking the Wnt co-receptor LRP5/6. Thus, in contrast of OPG, which specifically inhibits osteoclastogenesis, SOST and Dickkopf-related protein 1 (DKK1) exerting their inhibitory effects on osteoblastogenesis [39]. Therefore, SOST may play a key role in vascular and tissue calcification [34, 39]. Moreover, recent studies have been shown that SOST is linked to bone physiology and cardiovascular disease through the Wnt/β-catenin signaling pathway [34].

RANK / RANK ligand system

The interaction between RANKL and its receptor RANK is essential for the differentiation and bone resorbing capacity of the osteoclastes, as well as controlling mineralization process that is suitable for several physiological and pathological states. RANKL is a type II homotrimeric transmembrane protein that is expressed as a membrane-bound and a secreted protein, which is derived from the membrane form as a result of either proteolytic cleavage or alternative splicing [40]. Serum RANK/RANKL have been identified as candidate

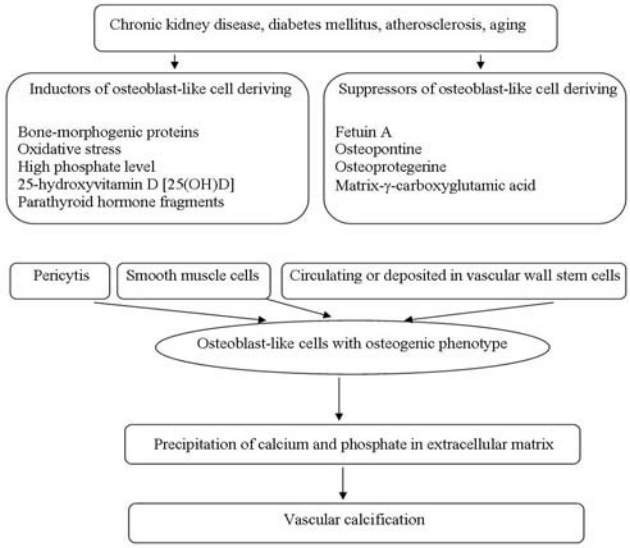

Figure 1: Vascular Calcification.

mediators for paracrine signaling in cell metabolism and extracellular matrix regulation but have also been shown to modulate dendritic cells and activated T cells, as well as to promote B-cell maturation and antibody response, which suggests a role in both innate and adaptive immunity [25, 26, 41]. There are various mutated RANKL proteins that abolish binding to OPG while preserving recognition of RANK [24]. Interestingly, the physiological RANKL/RANK interaction is not optimized for maximal signaling and function, perhaps reflecting the need to maintain receptor specificity within the TNF super family. Therefore, integrin β3, V-ATPase, CAII, CTSK, TNF receptor-associated factor (TRAP), MMP-9, parathyroid hormone, and hormonally active form of vitamin D3, 1α,25-(OH)2D3 have been identified as essential regulators of RANK / RANKL system activity [42, 43].

Biology of Ectopic Vascular Calcification

Contrary bone mineralization, vascular calcification is a pathological process, occurring in response to dysregulated or inappropriate changes in environmental metabolic factors [44, 45]. It results of imbalance between calcification inhibitors and promoters, which act at the systemic and the local level [46]. Therefore, this imbalance leads probably to phenotypic change of smooth muscle cells towards osteoblast-like calcifying smooth muscle cells, which mediate organized extracellular matrix deposition in the vascular wall [45, 47]. Figure 1 shows consequently mechanisms that directly and indirectly lead to ectopic vascular wall calcification. Overall there is a hypothesis that ectopic vascular calcifications could be mediated by pathophisiological mechanisms underlying bone biomineralization affected residence cells allocated in vascular wall. Indeed, calcified vascular tissue expresses bone-related proteins, bone specific transcription factors and bone morphogenetic proteins (BMPs), which contribute in osteogenesis in bone [28, 48]. However, the origin of calcifying cells directly promoted vascular tissue mineralization is still unknown. Vascular smooth muscle cells may differentiate into calcifying vascular smooth muscle cells keeping their own identity while using mechanisms that osteoblasts use to biomineralization in

Table 2: Promoters and inhibitors of vascular calcification.

Calcification promoters	Calcification inhibitors
Inflammatory interleukins [56]	Vitamin K-dependent Gla-rich protein [56]
TNF alpha and other inflammatory cytokines [80-82]	Matrix Gla protein [9, 47]
Osteocalcin [30]	Fetuin-A [35]
Bone-morphogenic proteins [28, 48]	VEGF [1, 6]
High phosphate level [46]	OPN [28]
Vitamin D [42]	OPG [57, 58]
Parathyroid hormone fragments [43]	Hyperglycemia [52]
Free reactive radicals and other components of oxidative stress [9]	Sclerostin [34, 39]
Sex steroids [7]	Dickkopf-related protein 1 [39, 60]
Osteocyte-derived sclerostin [8]	
Advanced glycosylation end-products [16]	
Klotho/fibroblast growth factor-23	

Abbreviations: TNF: Tumor Necrotic Factor; VEGF: Vascular Endothelial Growth Factor, OPN: Osteopontin; OPG: Osteoprotegerin.

nature manner entering an osteoblast-like differentiation program [49]. In fact that matrix metalloproteinases (MMP-2 and -9) are able to degradate elastin that leads to activation of MAPK signalling pathway and may result in the induction of Cbfa1/Runx2. All these sequentially initiate the transformation of vascular smooth muscle cells into osteoblast-like cells too. Therefore, it is known that over expression of extracellular matrix and biomineralization genes relevant for bone formation are sufficiently modulated by calcifying vascular smooth muscle cells [50]. Moreover, these genes constitute the strongest link between residence cells and pathological vascular remodelling phenotype associated with calcification of vascular wall [51]. Finally, ectopic artery mineralization is frequently accompanied by decreased bone mineral density or disturbed bone turnover [44]. Interestingly, type 2 diabetes mellitus (T2DM) associates with increased fracture risk despite the fact that T2DM patients have higher bone mineral density as compared to non-diabetic individuals. Therefore, there are evidences that T2DM might contribute to decreased bone formation through interference of advanced glycosylation end-products with osteoblast development, function and attachment to collagen matrix, increased levels of osteocyte-derived sclerostin, and hyperglycemia-induced suppression of osteogenic differentiation of marrow-derived progenitor cells diverting osteoblastic precursor cells [52]. Overall T2DM-dependend inflammatory process contributing to bone demineralization may lead fracture risk, but extra bone mineralization activity might increase. All these mediate augmented vascular calcification and promote atherosclerosis in T2DM patients. However, there are still unclear, whether is relationship between processes of bone and vascular calcification that appear to be inversely related [53]. Further examinations are needed to improve understanding of the precise mechanism in this area.

There is evidences regarding an activation of resident pericytes in the vascular wall may contribute vascular calcification [53]. Indeed, pericytes that are discussed as mesenchymal progenitor cells have the powerful potential to develop into osteoblasts and chondrocytes in situ under influence of inflammatory cytokines, oxidated lipids, free active radicals, turbulent blood flow, high pressure, shear stress, and growth factors contributed in angiogenesis and neovascularization [54]. Interestingly, neoangiogenesis that is suitable for atherosclerosis, malignancy may facilitate migration of pericytes and thereby induce vascular wall mineralization [55].

Bone-related Proteins and Bone-morphogenic Protein-2 in Atherosclerosis and Vascular Remodeling

Vascular calcification frequently appears in arterial wall due to atherosclerosis, inflammation, worsening of calcium homeostasis. Vascular calcification demonstrates increased prevalence in cardiovascular and chronic kidney disease, atherosclerosis and dyslipidemia [54]. Recent investigations have been shown that vascular calcification is a complex sophisticated pathological process affected promoters and inhibitors of calcification, resembling skeletal metabolism, and regulated by resident cells, intermediates, hormones, cytokines, and active peptides [56]. Therefore, atherosclerosis, low-intense inflammation, stretch-induce arterial wall hypertrophy, dyslipidemia are considered main factors that contribute in endothelial dysfunction and direct relate in clinical outcomes among subjects belong general and selective populations. The main inductors and suppressors of vascular wall calcification are reported in Table 2.

The key point of the beginning of vascular calcification is formation of osteogenic phenotype of target cells, i.e. pericytes, vascular smooth muscle cells, and probably stem cells. Osteogenic differentiation of target cells including vascular smooth muscle cells is characterized by the expression of bone-related molecules including bone morphogenetic protein (BMP)-2, Msx2, OPG and OPN, which are produced by osteoblasts and chondrocytes. Osteogenic transforming target cells produce hydroxyapatite, which includes in calcium deposition in extra bone sites including vascular wall, valvular leaflets, etc. Finally, calcium deposits of atherosclerotic plaque and vascular wall, which appear to be identical to fully formed lamellar bone, may worse mechanical and structural properties of vessel and lead to vascular complications. Although BMP-2 is currently recognized as the main factor in calcium-phosphorus metabolism disorders that leads to vascular calcification in patients with chronic kidney failure, the direct effect of BMP-2 on vascular integrity in other patient populations, i.e. heart failure subjects, patients with coronary artery diseases, asymptomatic atherosclerosis,

T2DM, obesity, subclinical and manifested hypothyreoidism, is still not fully understood and requires more investigations.

Recent data have linked RANKL and OPG to cardiovascular disease, including CHF, immunity, vascular calcification, osteoporosis, and bone remodeling [57-59]. Low-intense inflammation is being discussed as a powerful trigger of vascular remodeling and calcification realized through bone-related protein pathway. Recent clinical studies have shown that coronary atherosclerosis associates with a significant increase of OPG and with a trend towards a decrease of soluble RANKL and RANKL/OPG Ratio [60]. Therefore, C-reactive protein (CRP) that over expressed in atherosclerosis, dyslipidaemia, and other dysmetabolic states (diabetes mellitus, abdominal obesity, metabolic syndrome) and cardiovascular diseases (ischemic heart disease, heart failure, hypertension, etc.), may stimulate RANKL production in monocytes. The RANKL-stimulated expression of wide spectrum of transcription factors, i.e. TRAF6, p38 mitogen-activated protein kinases (MAPKs), JNK IκB-α, and NF-κB p65 DNA, triggers overproduction of bone-related proteins. Overall RANKL/RANK/OPG system and its downstream signaling pathway are closely controlled via inflammatory cytokine (TNF alpha, interleukin (IL) 1β, IL-6, IL-10, IL-21 and IL-23) productions [61, 62]. These effects may consider an important mechanism of endogenous protection from tissue injury. Indeed, recent animal studies have shown that OPG protects large arteries from medial calcification [63]. Therefore, lowed values of sRANKL/OPG ratio and increased OPG level frequently associate with vascular calcification in subjects with declined glomerular filtration rate, as well as in older patients and hemodialysis subjects [61]. Interesting, that increase of serum OPG and the age-dependent decrease of sRANKL concentration is not able to explain by the elimination of renal clearance only. Alterations in sRANKL/OPG ratio might reflect a compensatory mechanism to modulate bone remodeling and prevention of extra bone calcification in these patients. Overall, OPG is discussed a vascular protector [64] and a surrogate marker of early coronary vascular calcification in patients with known asymptomatic coronary artery disease, dysmetabolic disease [65].

OSN has found a causes myocardial hypertrophy, increased fibrillar collagen content, stimulates cell signaling, adhesion, survival, proliferation, and migration in several cell types, mediates calcification of the vascular wall, coagulation, and endothelial dysfunction [66]. Recent animal studies have been revealed that increased circulating OSN associates with higher incidence of mortality following myocardial infarction, due to increased rates of rupture and newly heart failure over the first 14 days after MI that associate with left ventricular dysfunction and increased mortality in short- and long-term period [67].

OPN is reported a surrogate marker of atherosclerotic lesions, especially in calcified plaques, is linked to the progression of coronary artery disease. Moreover, OPN is powerful biomarker of asymptomatic coronary artery disease [68] and vascular calcification in patients with chronic kidney disease [69] with possible predictive value. OPN has a renal clearance and demonstrates a closely interaction with glomerular filtration rate [70]. Recent studies have been shown that OPN and renal failure were the independent risk factors for coronary heart disease [71, 72]. There are evidences that OPN relates a systemic inflammatory activation and endothelial dysfunction that is considered a marker of negative clinical outcomes in cardiovascular disease. Finally, circulating level of matricellular proteins associates with vascular wall calcification, target organ damage including lowed kidney function, plaque formation, and endothelial dysfunction. However, the predictive role of these biological markers is not fully understood and requires more investigations.

The Role of Bone-related Proteins in Age-related Diseases

Bone has evolved to provide structural support to organisms, and therefore its mechanical properties are vital physiologically [13]. Bone remodeling is age-dependently regulated and changes dramatically during the course of development. Progressive accumulation of reactive oxygen species and hypoxia have been suspected to be the leading cause of many inflammatory and degenerative diseases, as well as an important factor underlying many effects of aging [8, 74]. However, the role of matricellular proteins and its co-regulators in age-related diseases is still under discussion and appears to be very controversial.

Osteopontin (OPN) and vascular endothelial growth factor (VEGF) are characterized by a convergence in function for regulating cell motility and angiogenesis, the response to hypoxia, and apoptosis [74, 75]. OPN and VEGF may co-express in age-related settings [76]. In vascular diseases, these two cytokines mediate remodeling, but may also perpetuate inflammation and narrowing of the arteries [77]. OPN and VEGF are elevated and contribute to vascularization in age-related manner [75]. Indeed, cyclic stretch as a main mechanical forces influencing vascular smooth muscle cells in vasculature, may initiate stimulates NADPH oxidase isoform 1 (Nox1)-derived ROS via MEF2B, leading to endothelail dysfunction via a switch from a contractile to a synthetic phenotype [77]. This process is up-regulated by OPN and down-regulated by calponin1 and smoothelin B. Thus, OPN-dependent pathway of vascular dysfunction bases on MEF2B-Nox1-ROS up-regulation under pathological stretch conditions suitable for hypertension. Indeed, stretch-induced Nox1 activation decreases actin fiber density and augments matrix metalloproteinase-9 activity, vascular smooth muscle cells migration [77]. All these fining may have a pivotal role for explanation of age-related hypertension. There are controversial data about age-related increasing of OSN. However, the diagnostic and predictive role of this fact is not clear and requires more studies.

Predictive Value of Bone-related Proteins in Patients after Stroke

The prognostic relevance of biomarkers related to atherosclerotic plaque calcification, i.e. OPN, OPG and RANKL was determined in several investigations. Interestingly that serum OPN may be a useful biomarker of atherosclerosis and vascular calcification. Importantly note that there was determined a positive association between circulating OPN and the presence of CAD but not the extent of coronary atherosclerosis [68]. Therefore, serum levels of OPN, but not OPG and RANKL peaked at day 7 after acute ischemic stroke and predicted worse neurological scores independently of age, gender, hypertension and thrombolytic procedures [78]. Whether serial measurements of OPN, OPG and RANKL are necessary for risk stratification of the patients after stroke is not clear.

Predictive Value of Matricellular Proteins in Heart Failure

Notwithstanding, bone-related proteins are considered a surrogate biomarker of vascular calcification in atherosclerosis, dyslipidemia, diabetes, obesity, etc., the role of sRANKL/OPG complex in maintenance of reparative repair potency among CHF persons shows to be a very intriguing while clinical data are limited. There are data OPG/RANKL/RANK system contributes to cardiac remodeling and left ventricular dilation after acute myocardial infarction in acute phase of cardiac failure as well as in chronic phase of heart failure development, while not so profoundly [79]. It is reported that serum RANKL was a significant determinant of NT-pro-BNP independent of age, BMI and creatinine clearance in CHF subjects [57]. There is interrelationship between OPG and serum RANKL concentrations in patients with advanced atherosclerosis in relation to medical history, risk factors and medication intake [80]. On the one hand, sRANKL/OPG complex contributes different stages in ischemic CHF development, whereas the clinical implication of RANKL seems uncertain [81]. On the other hand, the independent predictive value was determined for OPG only [82]. Finally, OPG is suggested to be a modulator rather than a marker of extracellular remodeling that may play critical role in CHF pathogenesis by neutralizing the effect of receptor activator of nuclear factor-kappa B ligand on differentiation and activation of wide spectrum cells, including circulating endothelial progenitor cells. The imbalance between free fraction of RANKL, calculated as sRANKL/OPG ratio, and circulating OPG may be responsible for the homeostatic mechanism of differentiation and apoptosis of endothelial progenitor cells [83, 84]. This effect may mediate overproduction of reactive oxygen species and oxidized lipoproteins through OPG-related activation of NOX-2 and NOX-4 and triggered phosphorylation of ERK-1/2 and p38 MAPK. All this mechanisms are suitable for ischemic CHF development. Results of the our study showed that components of sRANKL/OPG complex were increased in CHF patients when compared with none-CHF persons with stable coronary artery disease (CAD) as well as with healthy volunteers. Therefore, decreased circulating EPCs related CHF in CAD subjects were found also. However, sRANKL/OPG ratio when compared with other components of cytokines-induced bone-related proteins RANKL and OPG in ischemic CHF patients was not only significantly associated with parameters of neuroendocrine activation such as NT-pro-BNP and hs-CRP, but it closely effected on EPCs with proangiogenic phenotypes. It has been suggested that sRANKL/OPG complex affected reparative face of the pathogenesis of ischemic CHF through modulating count of circulating endothelial progenitor cells. Because OPG may stimulate differentiation of the endothelial progenitor cells and positively regulate their count in circulation, it has suggested that free fraction of serum RANKL, calculated as serum RANKL/OPG ratio, consider powerful predictor for depletion of CD14+CD309+ EPCs and CD14+CD309+Tie2+ endothelial progenitor cells in CHF patients. Probably, this effect may have a prognostic value for subjects with CHF. Overall the role of OPG as independent predictor of CHF development and progression requires detail investigations.

OPN has been demonstrated to be up-regulated in left ventricular hypertrophy, dilated cardiomyopathy, diabetic cardiomyopathy, and it is discussed a possible predictor of heart failure development and heart failure-related clinical outcomes [85]. OPN independently predicted all-cause mortality and acutely CHF-related readmission after 1 and 5 years [86, 87]. Moreover, compared with NT-proBNP, OPN was of superior prognostic value, specifically in acutely CHF patients and for the prognostic outcome of acutely CHF-related readmission [86]. However, the predictive value of peak OPN concentration and serial measurement of OPN in heart failure patients appears to be attractive. It is not clear whether declined OPN level within treatment of heart failure patients associates with better prognosis when compared with subjects with increased OPN concentration.

It is found the serum OSN in patients with CHF predominantly reflected a positive pro-inflammatory response and alterations in protein metabolism that leads to biomechanical stress [88]. However, the roles of OSN in the CHF have not been defined. Finally, further studies are needed to elucidate the potential role of bone-related proteins in the complex pathogenesis of heart failure.

Conclusion

Although there are not sufficient evidences that the clinical correlations of circulating levels of matricellular proteins in subjects with documented cardiovascular diseases might have predictive value, it has been suggested that exaggerated level of OPG and probably OPN and OSN would confer a better prognosis in CAD patients, especially those who are underwent revascularization procedures or have acute / acutely decompensated heart failure. By now there are evidences regarding an association of circulating bone-related proteins predominantly OPG and OPN with vascular calcification. Therefore, the negative effect of these proteins on progression of age-related diseases has been reported. Currently the continued monitoring for OPG / RANKL, OPN and OSN levels is not recommended, but patient from vulnerable populations at high cardiovascular risk, probably, may have some benefit in prediction of clinical outcomes based on serial assessment of circulating bone-related proteins.

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