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REVIEW PAPER

Osteopontin and cardiovascular system

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Abstract A matricellular protein, osteopontin (OPN), is expressed in response to mechanical stress and similar stimuli in the heart, integrates the inter-ECM signal transduction network of component cells, and maintains efficient contractility through quantitative and qualitative control of extracellular matrix (ECM) proteins. In particular, OPN is re-expressed in the process of tissue damage; combines with other cell growth factors, cytokines, chemokines, and proteases as a cytokine itself or as an adhesion molecule; and controls the differentiation and growth of cells involved in re-storation of tissues by controlling inter-cellular signal transduction and production of ECM proteins through regulation of expression levels and activity. A study using mice lacking a functional OPN gene indicated that tissue restoration fails and collagen deposition is inhibited through matrix metalloproteinases (MMPs) in mice lacking OPN. Thus, while OPN accelerates the cardiovascular remodeling process, it also regulates the balance of various inter-cellular activities. In addition, OPN not only promotes arteriosclerosis but is also closely associated with angiogenesis. With the roles of OPN expected to be clinically elucidated, the clinical use of OPN for control of cardiovascular remodeling may be feasible.

Points (1) Osteopontin (OPN) efficiently propagates contraction in the heart as a matricellular protein and thereby controls ECM proteins both quantitatively and qualitatively.
(2) The quantitative and qualitative control of ECM proteins is involved in interaction with OPN receptors including those of the integrin family, CD44, and others.
(3) OPN promotes myocardial remodeling through TGFβ and MMPs.
(4) OPN not only promotes arteriosclerosis but is also closely associated with arteriosteogenesis.
(5) In animals lacking OPN, tissue remodeling process is inhibited, especially in terms of fibrosis after myocardial infarction.
(6) While the significance of OPN as an immune system molecule is still unclear in detail, the significance of OPN in the regenerative immune system has begun to be determined.

Keywords Extracellular matrix (ECM) · Matricellular proteins · Osteopontin (OPN) · Remodeling

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What is osteopontin?

Extracellular matrix (ECM) proteins influence signal transduction into cells and ensure not only growth or transfer of cells, but also their existence by adhering to them. With the exception of cancer cells, cells are destined to die as programed if they dissociate themselves from ECM proteins (anoikis) [1]. Accordingly, it is believed that cells generate matricellular proteins to control adhesion with ECMs in accordance with their mobilization or shape change. Matricellular proteins, which are ECM proteins, appear to control cellular functions between cells and ECMs [2] without directly contributing to structure as a support base for tissues. OPN, a non-collagenous matricellular protein, is also

called transformation-specific secreted phosphoprotein (SPP-1) because it is newly secreted within cells in association with transformation caused by viruses or oncogenes with an integrin-binding sequence contained within the molecule, and early T lymphocyte activation (Eta-1) [3], because it is induced early after T-cell stimulation. OPN is a phosphorylated glycoprotein generated or secreted by osteoblasts, osteoclasts, macrophages, T-cells, hematopoietic cells, vascular smooth muscle cells, fibroblasts, myocardial cells, and other types of cells. It has been found that OPN is chiefly involved in cellular migration or infiltration in cellular immunity, restoration of tissues, and inflammatory diseases, as well as in angiogenesis, inhibition of cellular death, and reconstitution of ECMs in tumor metastasis [4]. Accordingly, it has come to be believed that OPN participates in integration of intercellular networks as a cytokine or humoral factor rather than merely maintaining structure. In addition, it is known that OPN is generated by macrophages, T lymphocytes, and NKT cells and converts the polarity of T-cells to Th1-type by generating IL-12 and IL-10. Thus, OPN is also involved in the onset of autoimmune diseases [5] including rheumatoid arthritis (RA) [6] and granulomatous diseases [7] including sarcoidosis. Table 1 shows the pathologies and diseases believed to be associated with OPN.

Protein/gene structure of osteopontin

Human OPN is a single-stranded polypeptide (314 amino acids) of approximately 32 kDa molecular weight with genes consisting of seven exons, located in the fourth chromosome (4q13) [8]. After being translated, OPN is phosphorylated by Ser/Thr kinase, sugar chains are added to it, and it is then secreted out of the cell. The post-translational modification level will vary among tissues and organs and depending on the time and the molecular weight will significantly change accordingly. Transcription is accelerated by growth factors [9] such as TGFβ, EGF, TNFα, PDGF, bFGF, and LIF1, cytokines (IL-1α and IL-2), retinoic acid, endothelin, and concanavalin A. In terms of the functional characteristics of OPN, while OPN adheres to cells with RGD amino acid sequences contained within it, it acts as a cytokine to promote the migration/growth potential of lymphocytes, macrophages, endothelial cells, and vascular smooth muscle cells. Figure 1 shows the relationship between the amino acid sequences and receptors of OPN. OPN is severed by thrombin into two pieces of approximately the same size as most of the functional domains located at the N terminus. OPN has 16 signal peptides in the N terminus and has Ser/Thr phosphorylation sites and a GRGDS motif [10], which are well preserved across species. The GRGDS motif is an extremely flexible molecule known to combine with at least eight types of integrins including $\alpha5\beta1$, $\alpha8\beta1$, $\alpha V\beta1$, $\alpha V\beta3$, and $\alpha V\beta5$ [11]. Immediately after the GRGDS motif, there exist SVVYGLR sequences that combine with integrins involved in causing inflammation. The linear sequence SVVYGLR directly binds to $\alpha4\beta1/\alpha9\beta1$ integrins and is responsible for $\alpha4\beta1/\alpha9\beta1$ integrin-mediated cell adhesion to the NH2-terminal fragment of OPN [12]. In addition to bonding with integrins, OPN also bonds with a hyaluronic acid receptor, CD44 in an RGD-independent manner, and induces macrophage chemotaxis, and engagement of ß3-integrin receptors [13]. On the other hand, OPN is severed by matrix metalloproteinase (MMP)-3 and MMP-7, which cleave OPN at sites close to or within the mapped integrin-binding sites [14]. As stated above, OPN is believed to have a wide variety of functions mediated by the numerous receptors that match OPN and changes in bonding patterns.

Table 1 Pathologies and diseases related to OPN

1. Malignancy—metastasis, angiogenesis
2. Chronic inflammatory diseases-atherosclerosis, colitis.
3. Immune system (auto-immune disease, delayed immunoreactivity) rheumatic arthritis, multiple sclerosischronic granulomatous disease (tuberculosis, sarcoidosis)
4. Urinary tract—nephrolithiasis, pyelonephritis
5. Wound healing (Tissue repair)—Cardiac Remodeling
6. Osteoporosis

Physiological significance of OPN in cardiac remodeling

Basic analyses

Osteopontin (OPN) is not expressed in healthy cardiac muscle tissue. Its expression is accelerated by mechanical stress including pressure/volume loading [15] and hypoxia. In addition, expression of OPN is accelerated by angiotensin II (AII) in rat cardiac fibroblasts [16]. OPN inhibits IL-1β-stimulated activities of MMP-2 and 9 in cardiac fibroblasts [17]. It was originally reported that OPN was expressed in infiltrating cells such as macrophages in interstitial tissues 1–3 days after myocardial infarction [18]. OPN expression was also observed in macrophage-like cells of inflammatory lesions in the cardiac muscle in a hamster model of cardiomyopathy [19]. Mice lacking osteopontin (OPN-/-) grow normally but deposit col-

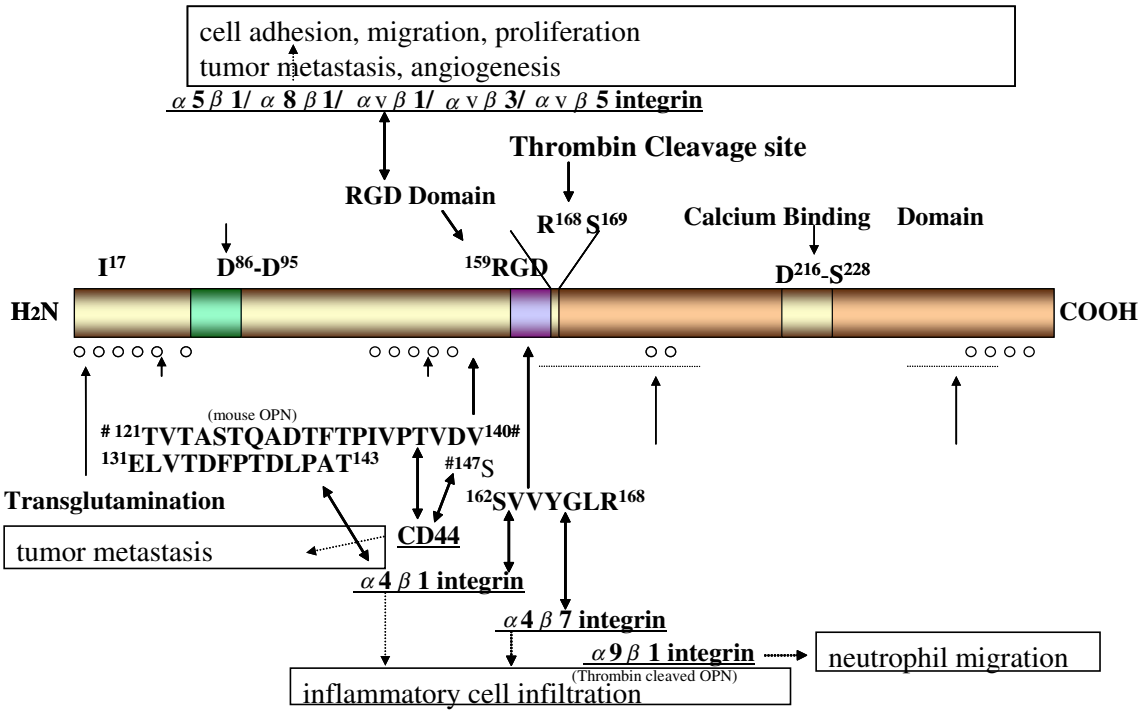

Fig. 1 Protein structure of and receptor for osteopontin. Human OPN consists of 314 amino acids and is severed by thrombin into two pieces with approximately the same size. A GRGDS motif (RGD domain) combines with at least eight types of integrins. OPN plays roles in cell adhesion, extension, and migration through the bonding of SVVYGLR sequences with $\alpha 4\beta 1/\alpha 9\beta 1$ integrins as a result of severance by thrombin

lagen in an abnormal manner with faulty wound healing [20]. In addition, OPN reduces p38 kinase, JNKs, Akt, and GSK-3 phosphorylation, which are related to cardiomegaly [21]. In models of myocardial infarction created using mice lacking OPN, the fibrosis accompanied by collagen deposition did not occur, and ventricular dilatation occurred. In particular, collagen deposition did not occur in association with type-I collagen hyperplasia [22]. The above findings support the hypothesis that OPN induce myocardial fibrosis and remodeling in the process of tissue repair following inflammation.

Thus, we examined the significance of OPN in a model of cardiac hypertrophy induced by AII using OPN-/-mice [23]. Wild-type mice (C57BL/6) and OPN-/-mice were administered AII (2 μg/kg/minute) for 4 weeks using osmotic pumps embedded in the back of the mice. Each group was measured for blood pressure, heart weight per body weight ratio, the transverse diameter of myocardial cells, and ratios of fibrosis in the perivascular and interstitial tissues; evaluated for left ventricular end-diastolic diameter (LVDd), %FS, and c-IRT by echocardiography; and evaluated for expression of OPN by the RT-PCR method and immunostaining and for apoptosis by TUNEL staining. It was found that administration of AII induced blood pressure elevation, cardiac hypertrophy, and perivascular and interstitial fibrosis in the wild-type mice (WT). In the OPN-/-mice, diastolic function was retained, with complete inhibition of perivascular and interstitial fibrosis (Fig. 2), although contractility decreased (Fig. 3). In the OPN-/-mice, macrophage infiltration in the cardiac muscle tissue caused by administration of AII and expression of eNOS and cytokine genes were decreased, as was collagen deposition and fibrosis, the ventricle dilated, and contractility decreased. The fibrosis in the myocardial remodeling system was originally considered a system activated by injured cardiac muscle to maintain structure. Accordingly, it was concluded that overexpression of OPN in the process of fibrosis by AII promotes remodeling and decreases the potential for dilatation, whereas lack of OPN results in failure of the fibrosis system itself and loss of contractility. Use of treatment strategies to control remodeling by optimization of OPN expression may be feasible.

Clinical perspectives on osteopontin

Stawowy et al. reported [24] in a study using myocardial biopsies obtained from 10 subjects with heart failure from dilated cardiomyopathy (DCM) that OPN

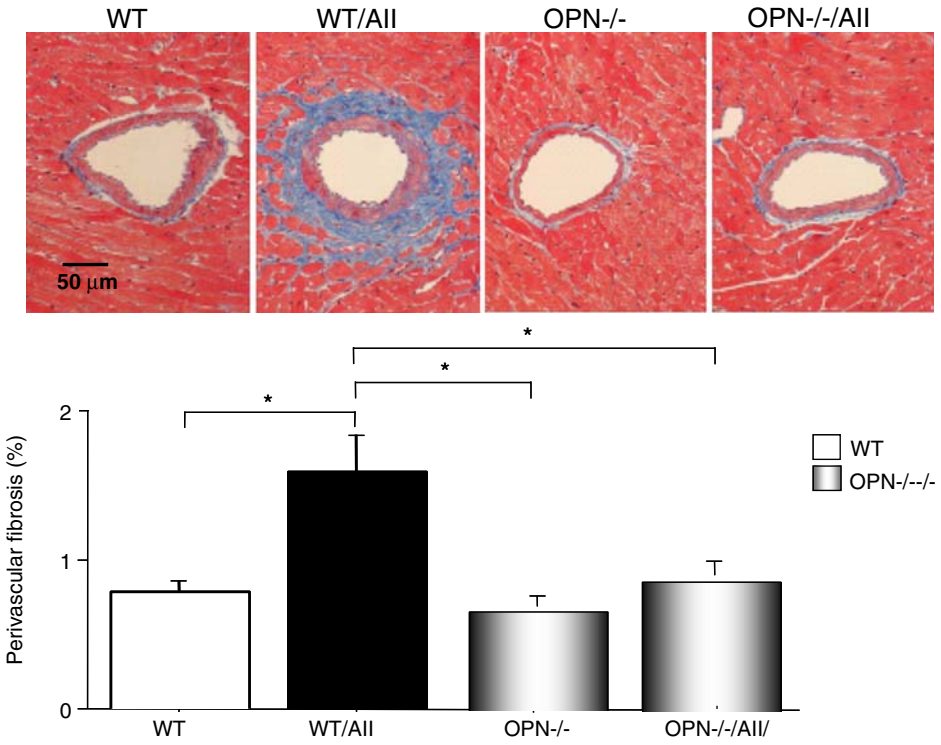

Fig. 2 Images of perivascular fibrosis of tissue in the heart. From the left, areas of fibrosis in wild-type mice (WT), wild-type mice administered AII (WT/AII), mice lacking osteopontin (OPN-/-), and mice lacking osteopontin administered AII (OPN-/-/AII)

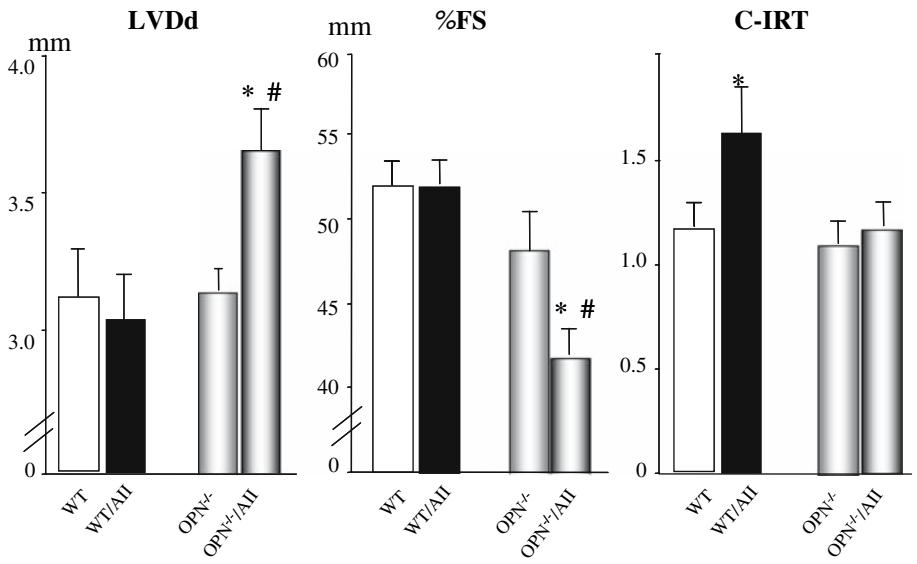

Fig. 3 Changes in cardiac function. From the left, left ventricular end-diastolic diameter (LVDd), left ventricular fractional shortening (%FS), and corrected isovolumetric relaxation time (C-IRT) in wild-type mice (WT), wild-type mice administered AII(WT/AII), mice lacking osteopontin (OPN-/-), and mice lacking osteopontin administered AII (OPN-/-/AII), respectively

was expressed in myocardial cells, and that this was related to cardiac hypertrophy and associated with decreases in LVDd and increase in ejection fraction. Sato et al. reported in a study using biopsies obtained from 51 subjects with DCM that OPN was expressed only in myocardial cells in association with changes in type-I collagen, LVDd, and ejection fraction [25]. We also studied OPN expression using myocardial biopsies from a group of patients with DCM, hypertrophic cardiomyopathy (HCM), and ventricular tachycardia. While neither OPN nor ANP was expressed in the group with normal hearts, OPN expression was detected in all ANP-positive cardiac muscle in the groups with DCM, HCM, or ventricular tachycardia, and this expression was related to area of myocardial fibrosis (Fig. 4). It has also been reported that OPN is expressed in association with severity of heart failure. Based on the finding that the level of OPN expression in the heart is associated with the area and severity of injury of cardiac muscle tissue, OPN may be a very

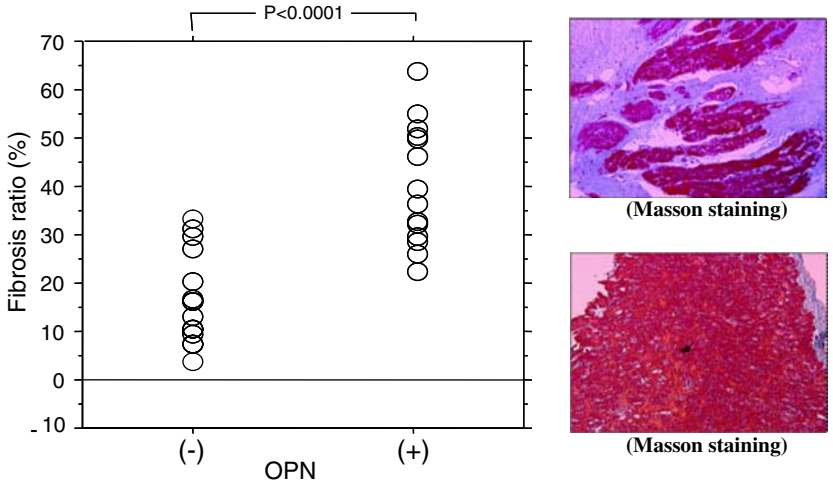

Fig. 4 Correspondence between fibrosis ratio and OPN expression in myocardial biopsy. Neither OPN nor ANP was expressed in the group of subjects with normal hearts. OPN expression was detected in all the ANP-positive cardiac muscle of the groups with DCM, HCM, or ventricular tachycardia, and this expression was related to area of myocardial fibrosis

useful index of myocardial repair processes as a CRP that reflects pathological activity.

Osteopontin in arteriosclerosis

Liaw et al. reported, in light of the findings that OPN was expressed in plaques in vascular smooth muscle cells, endothelial cells, and macrophages [26], that it was expressed in the neointimal growth process after intimal detachment in the carotid artery of rats [27]. Although it is still unclear whether OPN promotes or inhibits arteriosclerosis, early-stage arteriosclerotic lesions were induced in the proximal aorta of OPN-overexpressing mice administered a cholesterol-lowering diet [28]. In addition, a study creating double-knockout mice lacking apoE and OPN revealed that arteriosclerotic lesions were reduced with decrease in macrophage infiltration in mice homozygously or heterozygously deficient in OPN, indicating that OPN promoted arteriosclerosis [29]. On the other hand, while it is known that expression of OPN is increased in calcified lesions [30], such findings as that calcification is inhibited by phosphorylation of OPN, that calcification of a transplanted aortic valve is promoted in mice lacking OPN, and that vascular calcification is further promoted in mice crossbred from a mouse lacking MGP with abnormal calcification and a mouse lacking OPN [31], indicate that OPN inhibits vascular calcification.

Physiological significance of osteopontin in serum

It has been reported that serum OPN level is related to the onset of pulmonary plaque and pneumoconiosis in patients with asbestosis, and that a group of patients with mesothelioma had still higher serum levels of OPN [32]. However, high OPN levels are observed not only in association with the onset of mesothelioma in patients with asbestosis. It has been reported that patients with ovarian cancer also have high serum OPN levels [33]. In addition, it has been reported that, in patients with RA, OPN develops in fibroblasts of pannus infiltrating the synovial tissues, and the cartilage in particular, of patients with increased blood levels of OPN during the active phase. Thus, OPN is not always disease-specific. Suezawa et al. found that serum OPN level was increased even 2 weeks after the onset of acute myocardial infarction [34]. On the other hand, with the finding of a correlation between serum OPN level and severity of coronary artery diseases reported in patients with coronary artery disease and with an association between serum OPN level and the onset of coronary artery events reported in patients with angina pectoris [35], it appears that serum OPN level may be useful in diagnosing the severity of arteriosclerosis, ischemic heart disease, and heart failure.

However, there are problems associated with measurement of serum OPN level. First, the source organs or cells expressing or secreting serum OPN are not yet known. Second, since the mechanism of OPN solubilization is unknown, the correlationship between organs or cells and the blood level is unknown. Third, there exist OPN derived from many organs, the molecular weights of which vary depending on the level of phosphorylation of OPN in the blood, and the serusm OPN level recognized by antibodies may also vary significantly among recognition sites and types of antibodies. For example, an antibody that recognizes the entire length of OPN may indicate a different antibody from that indicated by an antibody that recognizes only the N or C terminus. In short, increase in the serum OPN level

may not always correspond to local increase in OPN production.

Consideration for the future

Bone and the immune system were originally believed to have too clearly different functions, with those of the former including preservation of the body and the skeleton and those of the latter functions such as prevention of infections. It was subsequently found that the skeletal system and the immune system are closly related, with the discovery of the osteoclast differentiation factors, RANKL (receptor activator of NF-κB) and TRANCE (TNF-related activation-induced cytokine). In 2000, Dr. Choi coined the term osteoimmunology [36] to indicate this relationship. OPN, which was also originally discovered in osteoblasts, has extremely diverse effects and may be a representative molecule in osteoimmunology that plays significant roles in the immune system as well. In the case of cardiovascular remodeling, while the significance of OPN as supportive tissue is gradually being revealed, little has been known yet for the significance as an immune system molecule except for the significance as a molecule forming granulation as a result of generation of excessive Th1 tissue responses in heart sarcoidosis. With the findings that OPN is involved in angiogenesis through the induction of the transcription factor Ets-1 and that OPN is involved in formation of niches in the bone-marrow-derived stem cells mobilization system or in differential inhibition of bone marrow stem cells, the significance of OPN in the regenerative immune system has begun to be clarified. Future developments in the study of OPN should thus be of great interest.

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