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PHYSIOLOGICAL IMPORTANCE OF OSTEOPONTIN

Dr. Dullo Puja,

Associate Professor, Natural Science Department

Oman Medical College
Bausher, Sultanate of Oman
P.O.Box-620, Postal Code: 130
Azaiba, Muscat,
Sultanate of Oman

Tel: (00968) 24504608 Ext : 160
Mobile : (00968) 99809360
E-Mail – puja_dullo@yahoo.com

ABSTRACT

Osteopontin a recently discovered ubiquitous glycoprotein secreted from various cells of the body. It has been found to anchor to bone cells to mineralize the bone matrix. As per some researches its uropontin form has shown to reduce growth of calcium crystals in the mice renal system; yet others suggest opposite role of this molecule in- vitro. Its modified form has great functional role in immune system by acting as a modulator in variety of manners other than regulating apoptosis. It plays important role in immigration of neutrophil and migration and degranulation of the mast cells. Its role in VSMC growth has well been demonstrated by various in-vivo and in- vitro experiments. Its versatile importance in respiratory physiology, cancer metastasis has been proved but many more physiological and clinical functions are still hidden which researchers are trying to find out for the treatment modality in near future.

KEY WORDS : Osteopontin, Immune system, Vascular smooth muscle cell growth

INTRODUCTION

Over last one decade many new important small molecules have been discovered. These molecules have different physiological role to play in our body. Their deficiency or absence will lead us into a pathological state. Out of all these new up coming components the one with diverse presence and different physiological role to play in body is Osteopontin (OPN). Osteopontin is acidic, phosphorylated sialic acid rich calcium binding 314 amino acid glycoprotein found in body fluids [1] and extracellular matrix component first identified in 1986 in Osteoblast cell by Oldberg et. Al., [2]

The human gene mapped for this small glycoprotein is on chromosomes 4q. Its receptor protein contains an Arg-Gly-Asp sequence which serves as a cell adhesion sequence that recognizes various integrins[3]. It is synthesized not only by fibroblast[4] , proosteoblasts, osteoblasts or

osteoclastic cell in bone but also are found in kidney, expressed in the bone marrow derived granulated metrial gland cells of the decidum and placenta and in number of specialized epithelial tissues which includes uterine epithetlial, sensory epithelial of the embryonic ear, smooth muscle cells[5], skeletal muscle myoblasts[6], dendritic cells and macrophages[7], other than hypertrophied chondrocytes and odontoblasts.

It has been proved experimentally that hypocalcemia and hypophosphatemia (instances that stimulates kidney's proximal tubule cells to produce calcitriol i.e., 1α, 25-dihydroxy vitamin D3) leads to increase OPN transcription, translation and secretion[8]. This is due to presence of a high- specificity VitaminD response element (VDRE) in the OPN gene promoter. Extracellular inorganic phosphate (ePi) has also been identified as a modulator of OPN expression [9].

Physiological function in Bone Remodeling:

OPN plays a role in anchoring osteoclasts to the mineral matrix of the bone[10]. 20% of dry weight of organic part of the bone has collagen Type I, osteocalcin, osteonectin bone sialoprotein and alkaline phosphatase other than OPN.

OPN serves to initiate the process by which osteoclasts develop their ruffled borders to begin bone resorption [10]. Since it is a product of cells in the osteoid matrix and can form a bridge (Latin Pons) between cells and the mineral[2] in the matrix, it was named "Osteopontin".

Role in inhibiting or promoting Renal Stone formation:

The majority of the human urinary stones are primarily composed of calcium salts. Although normal urine is frequently supersaturated with respect to calcium oxalate, most individuals do not form stones. This suggests that there are some factors inhibiting urinary stone formation. Uropontin, the urinary form of OPN has been shown previously to reduce growth[11] and aggregation[12] of calcium oxalate crystals and block the binding of the crystals to renal epithelial cells[13].

Uropontin inhibits calcium oxalate monohydrate (COM) growth and aggregation. In addition OPN also favors formation of calcium oxalate dehydrate (COD) over COM crystals in vitro. COD is less adherent to renal epithelial cells than COM[14].

Some reports suggest that OPN plays an important role in the process of stone formation. In vitro, the 45Ca concentration in calcium oxalate crystals adhering to Madin- Darby canine kidney (MDCK) cells was about 1.4 times in MDCK cells incubated with OPN than in a control group, and was about one half that in MDCK cells incubated with thrombin than in the control group[15].

Role in Immune function:

Full length OPN (OPN-FL) can be modified by thrombin cleavage, which exposes acryptic sequence, SVVYGLR on the cleaved form of the protein known as OPN-R.This cleaved OPN exposes an epitope for integrin receptors of α4β1, α9β4 and α9β1[16] and these receptors are present on a number of immune cells such as mast cells[10], neutrophils[17] and T cells. They are also expressed by monocytes and macrophages[18].

OPN is reported to act as an immune modulator in a variety of manners[3]. Firstly, it has a chemotactic property, which promotes cells recruitment to inflammatory sites. It also functions as an adhesion protein, involved in cell attachment and wound healing. In addition, OPN mediates cell activation and cytokine production.It is well known from promoting cells survival by regulating apoptosis[3].

OPN is important for the immigration of neutrophil in –vitro[19]. OPN recruits inflammatory cells to arthritis joints in the collagen- induced arthritis model of rheumatoid arthritis[20]. It has been found that OPN plays a role in mast cell migration and its degranulation[21] by observing decreased level of chemotaxis in the cells which were OPN knock- out mast cells compared to wild type mast cells in culture medium. OPN was also found to act as a macrophage chemotactic factor[22]. In this study, researchers looked at the accumulation of macrophage in the brain of Rhesus monkeys and found that OPN prevented macrophage from leaving the accumulation site, indicating an increased level of chemotaxis.

Cell Activation:

OPN inhibits production of Th2 cytokine IL-10, which leads to enhanced Th1 response. OPN influences cell- mediated immunity and has Th1 cytokine function. It also enhances B cell immunoglobin production and proliferation[3.]

Apoptosis:

OPN is an important anti-apoptotic factor in many circumstances. It blocks the activation – induced cell death of macrophage and T cells as well as fibroblasts and endothelial cells exposed to harmful stimuli[23,24]. OPN prevents non programmed cell death in inflammatory colitis[25].

Role in Vascular smooth muscle cell VSMC Remodeling:

OPN is a matrix molecule and its expression is dramatically increased by Angiotensin II. OPN has been shown to exert important effect on VSMC growth[26]

Remodeling process of VSMC is increased at mRNA and protein levels after addition of Angiotensin II to rats' cardiac fibroblasts. This suggests that ANF II regulates cardiac fibroblast behavior in cardiac remodeling process thus suggesting that OPN contributes directly to contractile dysfunction seen in the model and in the blood pressure independence[27].

OPN induces both medial thickening without injury and neointimal formation after injury suggesting acertain role in the development of vascular remodeling after angioplasty in –vivo[28]. This small molecule is one of the most hightly induced proteins at sites of epithelial injury[29]. OPN appears to specifically promote early inflammatory mechanisms associated with macrophage recruitment in atheroscleorotic lesions[30].

Role in muscular regeneration:

It has been shown by a study that myoblast cells release osteopontin to assist in controlling both the myogenic and inflammatory processes during the early stages of muscle regeneration[31].

Role in respiratory system:

OPN being a cytokine component which upregulated epithelial cells and macrophage in the lungs during chronic allergen challenge and airway remodeling. The data reveals it is a novel therapeutic target for airway remodeling and associated airway hyper-responsiveness (AHR) in chronic asthama[32].

Clinical Application:

OPN interacts with multiple cell surface receptors which are ubiquitously expressed making it an active player in many physiological and pathological processes; like in wound healing, bone turnover, ischemia, immune responses and tumorgenesis. By manipulating plasma OPN levels its usefulness in the treatment of autoimmune disease like Rheumotoid arthritis, multiple sclerosis, cancer metastasis, osteoporosis and some stress forms might be possible[2].
Research is still going on regarding Osteopontins' physiological, pathological and clinical abilities.

REFERENCES

1. "The Early Detection Research Network" Translational Research to Identify Early Cancer
2. OldbergA, FranzenA, HeinegardD. "Cloning and sequence analysis of rat bone Sialoprotein (osteopontin) cDNA reveals an Arg-Gly-Asp cell binding sequence." Proc Natl Acad Sci USA: 83; 8819-23: 1986.
3. WangKX, DenhardtDT. "Osteopontin: role in immune regulation and stress responses." Cytokine Growth Factor Rev.19 (5-6):333-45, 2008.
4. AshizawaN, GrafK, DoyS, et. Al., "Osteopontin is produced by rat cardiac fibroblasts and mediates A (II)- induced DNA synthesis and collagen gel contraction." J.Clin.Invest.98(10) : 2218-27;1996
5. IkedaT, ShirasawaT, EsakiY, YoshikiS, Hirokawak. "Osteopontin mRNA is expressed by smooth muscle- derived foam cells in human atherosclerotic lesions of the aorta." J.Clin.Invest; 92(6): 2814-20: Dec1993
6. UaesonontrachoonK, YooHJ, TudorE, PikeRN, MackieEJ, PageICN." Osteopontin and skeletal muscle myoblasts: Association with muscle regeneration and regulation of myoblast function in vitro". Int.J.Biochem.Cell Biol. 40 (10): 2303-14; April 2008.
7. MurryCE, GiachelliCM, SchwartzSM, VrackoR." Macrophages express osteopontin during repair of myocardial necrosis." Am.J.Pathol; 145(6): 1450-62; Dec 1994.
8. YuchaC, GuthrieD." Renal Homeostasis of Calcium." NephrolNarsJ; 30(1): 755-64; Dec2003.
9. FatherazisS, Matsa-DunnD, FosterBL, RutherfordRB, SomermanMJ, PreslandRB." Phosphate regulates osteopontin gene transcription." J.Dent. Res; 88(1): 39-44; Jan2009.

10. ReinholtFP, HultenbyK, OldbergA, HeinegardD.” Osteopontin ---- a possible anchor of osteoclasts to bone.” Proc. Natl.Acad.Sci. USA; 87(12): 4473-5; June 1990.

11. ShiragaH, MinW, VanDusenWJ, et.,al.”Inhibiion of calcium oxalate crystals growth in vitro by uropontin: Another member of the aspartic acid- rich protein superfamily.” Proc. Natl Acad Sci. USA; 89: 426-430; 1992.

12. AsplinJR, ArsenaultD, ParksJH,etal.,” Contribution of Human uropontin to inhibition of calcium oxalate crystallization .” Kidney Int;53: 194-199; 1998.

13. LieskeJC, LeonardR, TobackFG.”Adhesion of calcium oxalate monohydrate crystals to renal epithelial cell in inhibited by specific anions.” Am.J.Physiol; 268: F604-612;1995.

14. Wessonja, WorcesterEM, WiessnerJH, et al.,”Control of calcium oxalate crystal structure and cell adherence by urinary macromolecules .” Kidney Int; 53: 952-957; 1998.

15. YamateT, KohriK, UmekawaT., et al.,” The effect of osteopontin on the adhesion of calcium oxalate crystals to Madin-Darby canine kidney cells.” Eur Urol; 30: 388-393; 1996.

16. SeiffgeD.” Protective effects of monoclonal antibody to VLA-4 on leukocytes adhesion and course of disease in adjuvant arthritis in rats.” J.Rheumatol; 23(12): 2086-91; Dec 1996.

17. BanerjeeA, ApteUM, SmithR, RamaiahSK.”Higher neutrophil infiltration mediated by osteopontin is a likely contributing factor to the increased susceptibility of females to alcoholic liver disease.” J.Pathol; 208(4): 473-85; Mar 2006.

18. SodekJ, BatistaDaSilvaAP, ZoharR.”Osteopontin and mucosal protection.” Dent. Res; 85(5): 404-415; May2006.

19. KohA, DaSilvaAP, BansalAK, BansalM, SunC,LecH, GlogauerM, SodekJ,ZoharR.” Role of osteopontin in neutrophil function.” Immunology; 122(4): 466-75; Dec 2007.

20. SakatM, TsuruhaJI, /Masuko-HongoK, NakamuraH, MatsiuT, SudoA,NishiokaK, KatoT.” Autoantibodies to osteopontin in patients with osteoarthritis and rheumatoid arthiritis.” J.Rheumatol; 28(7): 1492-5; July2001.

21. NagasakaA, MatsueH, MatsushimaH, etal. ” Osteopontin is produced by mast cells and affects IgE-mediated degranulation and migration of mast cell.” Euro.J.Immunol; 38(2):489-99; Feb2008.

22. Burdo T H, Wood M R, Fox H S.” Osteopontin prevents monocyte recirculation and apoptosis.” J. Leukoc. Biol; 81(6):1504-11; June 2007.

23. Denhardt D T, Noda M, O’ Regan A W, Pavlin D, Berman J S.”Osteopontin as a means to cope with environmental insults: regulation of inflammation, tissue remodeling, and cell survival.” J. Clin. Invest; 107(9): 1055-61; May2001.

24. Standal T, Borset M, Sundan A." Role of osteopontin in adhesion, migration, cell survival and bone remodeling." Exp. Oncol; 26(3): 179-84; Sep2004.

25. Da Silva A P, Pollett A, Rittling S R, Denhardt D T, Sodek J, Zohar R." Exacerbated tissue destruction in DSS- induced acute colitis of OPN-null mice is associated with down regulation of TNF- alpha expression and non- programmed cell death."J. Cell. Physiol; 208(3):629-39; Sep2006.

26. BradfordCB." Vascular smooth muscle growth: Autocrine growth mechanisms." Physiological Reviews; Vol81(3); July2001.

27. PaulM, Mehr AP, KreutzR."Physiology of local Renin –Angiotensin systems." Physiol. Rev; Vol 86: 747-803;July 2006.

28. Infanger M, Shakihae M, KossmehlP,et., al."Intraluminal application of vascular endothelial growth factor enhances healing of microvascular anastomosis in a rat model." J Vasc Res;42:202-21; 2005.

29. SheppardD."Function of Pulmonary epithelial integrins: from Development to disease." Physiol Rev ;83:673-86;2003.

30. Tedgui A, Mallat Z."Cytokines in artherosclerosis: Pathogenic and regulatory pathway." Physiol Rev ;86:515-81;2006.