Bone 81 (2015) 7–15

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Review

Interactions between osteopontin and vascular endothelial growth factor: Implications for skeletal disorders

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ARTICLE INFO

Article history:
Received 27 November 2014
Revised 9 February 2015
Accepted 8 May 2015
Available online 27 June 2015

Keywords:
Bone
Healing
Remodeling
Microgravity
Kidney
Angiogenesis
Hypoxia
Apoptosis

ABSTRACT

Osteopontin (OPN) and vascular endothelial growth factor (VEGF) are characterized by a convergence in function for maintaining the homeostasis of the skeletal and renal systems (the bone–renal–vascular axis regulates bone metabolism). The two cytokines contribute to bone remodeling, dental healing, kidney function, and the adjustment to microgravity. Often, they are co-expressed or one molecule induces the other, however, in some settings OPN-associated pathways and VEGF-associated pathways are distinct. In bone remodeling, OPN and VEGF are regulated under the influence of growth factors and hormones, hypoxia and inflammation, the micro-environment, and various physical forces. Their abundance can be affected by drug treatment. OPN and VEGF are variably associated with kidney disease. Their balanced levels are critical for restoring endothelial cell function and ameliorating the adverse effects of microgravity. Here, we review the relevant 83 papers of 257 articles published, and listed in PubMed under the key words OPN and VEGF.

Contents

1. Introduction

For this comprehensive review, 257 articles with the key words "osteopontin" or "OPN" and "vascular endothelial growth factor" or "VEGF" in PubMed were screened (time frame from year 1996 to year 2014) (Fig. 1). After the exclusion of 37 papers, which did not focus on

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http://dx.doi.org/10.1016/j.bone.2015.05.047
8756-3282/

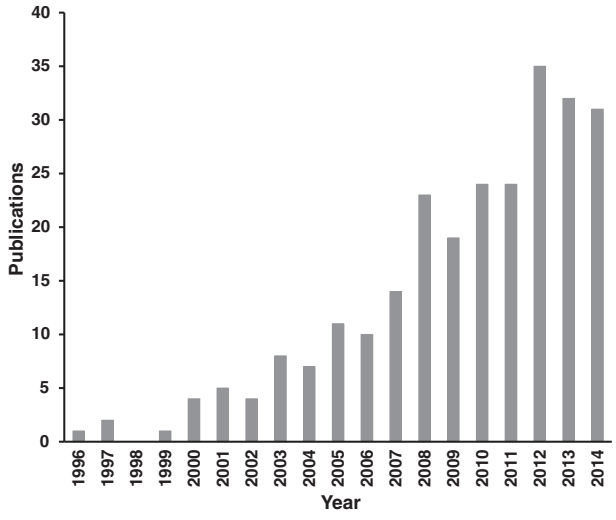

Fig. 1. Publication statistics. Papers on OPN and VEGF by publication year.

the interactions between these molecules, 220 articles were selected. Publications pertaining to cancer are covered elsewhere [1]. Here, we discuss the references relevant to the skeletal and renal systems. Together, our two reviews cover the currently available literature on the subject.

2. Skeletal healing and remodeling

Throughout the processes of osteoblast differentiation, matrix mineralization, tissue repair and bone regeneration, the expression and levels of OPN and VEGF vary (Table 1) [2–16].

- During bone development, these cytokines contribute to osteogenic differentiation and matrix mineralization [17]. VEGF stimulates osteoblastic differentiation. OPN is present as one of the important non-collagenous components of the extracellular matrix and is generated by osteoblasts prior to matrix mineralization.
- OPN and VEGF contribute to tissue repair. Most relevant growth factors and extracellular matrix-associated gene products are elevated in the repair phase during intra-membranous bone regeneration. OPN and VEGF levels are up-regulated in the first few weeks after long bone fractures, accompanied by severe endothelial dysfunction. While OPN levels fall back to normal in parallel to the fracture healing process, VEGF remains up-regulated for a month during the remodeling phase, even after full recovery, thus establishing its possible role in osteoclastic activity [18,19]. Stress or fatigue fractures are incomplete, non-displaced fractures that occur following repetitive loading, rather than a single traumatic event. Stress fracture healing leads to a significant up-regulation of OPN, VEGF, osteoprotegerin, cyclooxygenase-2, and RANK ligand over unloaded healing, suggesting roles for these molecules in the remodeling process [20].

2.1. Growth factors and hormones

Various growth factors and other proteins that are important for bone formation affect the expression levels of OPN and VEGF. Bone morphogenic proteins are of critical importance. During osteoblast progenitor cell differentiation in bone marrow stromal cells, exogenous bone morphogenetic protein (possibly provided by native bone marrow stem cells transduced with BMP-2 and VEGF [21]) increases time-dependently the mRNA levels of both VEGF and OPN along with other bone matrix proteins and osteoblast-related genes (type I collagen, alkaline phosphatase, osterix, osteocalcin, and parathyroid hormone receptor), thus enhancing osteo-inductivity, bone matrix formation, and mineralization. VEGF, secreted by osteoblasts in response to bone morphogenetic protein, is involved in coupling angiogenesis to bone formation [17]. The bone morphogenic protein BMP-2 also enhances ectopic bone formation by recruiting circulating bone marrow-derived osteoblast progenitor cells via CXCR4/SDF-1 interaction at the site of BMP-2 secretion. These circulating progenitor cells express CD44, a receptor of OPN, and their interaction likely contributes to the process (of note, OPN may upregulate CXCR4/SDF-1 signaling [22]). Simultaneously, the VEGF levels in muscular tissue surrounding the source of BMP-2 are elevated, thus suggesting a possible contribution by VEGF to angiogenesis at the site of bone regeneration [23]. TGF-β signaling is important for ossification and chondrocyte differentiation. In the absence of its type II receptor, the expression of OPN and VEGF is lowered and terminal differentiation is delayed [24]. The effects of osteoinductive growth factors (BMP-2 and TGF-β1) may be enhanced by thermal stress preconditioning. Together they elevate the expression of OPN and VEGF along with osteocalcin, osteoprotegerin and cyclooxygenase 2 (COX-2), thereby speeding up the process of bone regeneration and healing as compared to heating or growth factor addition alone [25]. Matrix vesicles, small molecules and plasma components may stimulate osteogenesis. Their actions involve bone morphogenic proteins as critical mediators. Matrix vesicles, present at the initiation site of calcification in all skeletal tissues, carry morphogenic information to nearby osteoblasts and chondrocytes in the form of osteogenesis promoting agents, including bone morphogenetic proteins (BMPs)-1 through -7 and angiogenesis stimulating proteins like VEGF and OPN (which also recruits osteoclasts during the bone resorption process). Other non-collagenous matrix proteins, including bone sialoprotein, osteonectin as well as osteocalcin, contribute, thus promoting skeletal cell differentiation and bone formation [26]. To accelerate bone healing, BMP-2 (maybe in conjunction with VEGF or TGF-β1) may be given directly [17,27], after thermal stress preconditioning [25], in vesicles [26], through the transduction of stem cells [21], or by implant coating [28].

Precursor cells contribute importantly to osteogenesis. Cord blood cells have mesenchymal multi-potency, and under lineage-specific stimulation may differentiate into osteoblasts, chondroblasts and adipoblasts. They are thus an attractive source for the treatment of musculo–skeletal defects in tissue engineering. Upon stimulation of cord blood stem cells with an osteogenic environment (consisting of dexamethasone, β-glycerophosphate and ascorbic acid) on a collagen I/III scaffold for three weeks, the expression of osteogenic markers including OPN, osteonectin, bone sialoprotein, collagen I and alkaline phosphatase increases along with the angiogenic marker VEGF [29]. The same mixture induces in embryonic stem cells a gene expression pattern similar to osteoblastic progenitors [27]. The intravenous transplantation of allogeneic mesenchymal stem cells increases OPN and VEGF mRNA expression and improves bone regeneration and angiogenesis in avascular necrosis of the femoral head [30]. Upon stimulation with platelet-rich plasma, the expression of both VEGF and OPN along with other bone matrix proteins increases in bone marrow cells, thus enhancing osteogenesis and angiogenesis during the wound healing process [31].

The SIBLING protein (small integrin-binding ligand, N-linked glycoprotein) matrix extracellular phosphoglycoprotein (MEPE) alters the expression levels of both OPN and VEGF via its effects on the bone–renal axis and on bone metabolism. Its overexpression is correlated with a reduction in circulating and urinary OPN and urinary calcium-phosphate levels, thus decreasing diet-induced renal calcification. It is also responsible for bone–renal neovascularization via an increase in VEGF expression coupled with increased aldosterone levels [32].

Platelet-derived growth factor (PDGF) is a critical factor involved in bone formation and an important regulator of signal transduction in mesenchymal cells. While its function is commonly linked to OPN, its interactions with VEGF are much more limited. Platelet-derived growth