Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology

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

Review article

Signaling of endothelin involves bone and soft tissue remodeling by modulating wound healing and tumor progression

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ARTICLE INFO

Article history:
Received 22 June 2016
Received in revised form 29 August 2016
Accepted 14 September 2016
Available online xxx

Keywords:
Endothelin
ET axis
New bone formation

ABSTRACT

Objective: The present review describes endothelins (ETs) and endothelin receptors (ETRs) involved in the remodeling of mesenchymal tissue and bone formation, as processes of wound healing and skeletal tissue remodeling.
Methods: We reviewed 136 manuscripts and papers, concerning about ET and ETR, how (1) ET and ETR stimulate osteoblastic activities, (2) P^{42}/P^{44} MAP kinase activation is mediated in ET-1-induced IL-6 synthesis, (3) ET induces Ca^{2+} mobilization and the activation of protein kinase C, (4) ET-1 regulates phosphorylation of connexin-43, and connexin-43 is predominant in the differentiation of osteogenic cells, and (5) ET inhibited the mutual process of osteoblasts.
Results: Since the discovery of ETs and ETRs, the vascular physiology and biological mechanism of ETs and ETRs have been highlighted and have indicated that ET-1 mediates the proliferation and differentiation of osteoblastic (progenitor) cells. ET-1 binds to ET_AR and osteoblasts, osteoclasts, and chondrocytes reactive to ET-1 mRNA, and ET-1 production by these cells are enhanced by BMP-7. ET exhibits a mitogenic function in connective and bone tissues. ET recognizes angiogenesis with VEGF, and cooperative ET may play a role in osteogenesis *via* matrix formation. Metastatic tumor cells produce ET-1, which stimulates new bone formation; this finding involves osteoblastic tumor metastases, a process that inhibits ET_AR antagonists. Understanding the multiple biophysiological functions of the ET axis is beneficial for application of new treatment employing tissue regeneration.
Conclusion: ET is one of the potent mediators of bone regeneration and morphogenesis, including skeletal formation, in craniofacial development.

Contents

☆ AsianAOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

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http://dx.doi.org/10.1016/j.ajoms.2016.09.002
2212-5558/

1. Introduction

Previous studies have shown that endothelin is one of the potent mediators of bone regeneration and morphogenesis, including skeletal formation, in craniofacial development [1]. When living bodies undergo trauma or injury, tissues or organs react by remodeling, and such a regular remodeling system has been referred to as wound healing. Tissue repair in connective tissue and bone is a highly coordinated process in which mesenchymal stem cells are recruited to form mature connective tissue, vascular tissue, cartilage, and bone. In the case of osteogenesis, vascular invasion and undifferentiated mesenchymal (homologous or stem) cells become committed to the osteoblast lineage and phenotypic characteristics associated with osteoblast activity following cartilage formation. In the early process, capillary vessel infiltration of newly-formed tissue is known to be crucial for osteoblast maturation and bone formation, and osteoblasts are located in close proximity or adjacent to newly-formed capillary vessels and are oriented in such a way that they secrete extracellular matrix (ECM) proteins (osteoid) in a directional manner. These mechanisms of ECM production from osteoblasts or osteoprogenitor cells have been reported previously. However, the mechanisms by which vascular cells influence function at osteoblast positions have not yet been delineated, but are known to involve the secretion of inductive factors such as endothelial-1 (ET-1) by vascular endothelial cells. ET is known to be biosynthesized in endothelial cells [2].

ET has been hypothesized to stimulate the proliferation and mineralization of osteoblastic (progenitor) cells, but also conversely inhibits the mineralization of osteoblastic cells. Thus, at present, the exact biophysiological roles of ET and ETR in the bone remodeling system including mineralization remain unknown. ET has been reported to stimulate bone resorption and anabolism as collagen and non-collagen protein synthesis [3]. ET_A and ET_B receptors were previously shown to be expressed on osteoblasts [4], and ET-1 stimulated DNA synthesis and reduced alkaline phosphatase activity [5]. ET-1 was also shown to bind to the ET_A receptor with intracellular signaling in osteoblastic-like cells (MC3T3E1 cells) [6–8]; however, ET_B receptors have also been implicated in ET-1-induced PLC activation. Recent studies have shown that bone tissue cells including osteoblasts, osteoclasts, and chondrocytes are reactive for ET-1 mRNA [9]. ET-1 production in these cells was shown to be enhanced by BMP7, but not TGF-β1 [10]. Contradictory results regarding the mitogen effect of ET have been reported showing either the inhibition [4,11] or promotion of osteoblastic differentiation by ET-1 [12,13]. The present review describes the biophysiological roles (enhancement or inhibition) of ET and ETR in remodeling tissue; connective tissue, chondrocytes, and osteoprogenitor cells to mature cells and final mineralization in matured bone. Excellent reviews have reported the biophysiological roles of ET, ETR, and endothelin-converting enzymes, and information on the basic biological functions of ET-related substances has been introduced [14–17].

2. Biophysiology

Endothelin (ET) has been classified into 3 isopeptides, ET-1, ET-2, and ET-3, with three corresponding chromosomal loci, and exist in human, porcine, and rat genomes. ET is composed of a 21-amino acid peptide (2.5 kDa), and ET-1, 2 and 3 are closely related isoforms, and differ in a few of the amino acid constituents, then the biological roles of ET-converting enzyme (ECE) and expression of ET_AR and ET_BR have been reported previously [18–22]. The biosynthesis and gene expression of ETs have also been described. Transmembrane signaling of ETs, ET binding sites, the phosphoinositide cascade, Ca^{2+} signaling, and the key roles of ETs were shown to be involved in the regulation of cellular signaling to specific cells or tissues [20]. We would emphasize ET-1 in this paragraph, because of ET-1 is the most major isoform and widely expressed in the human cardiovascular system. Endothelin-converting enzyme (ECE-1) catalyzed the proteolytic activation of Big ET-1 to ET-1 *in vitro* [23]. ECE exists in isoforms localized intracellularly in endothelial cells and this enzyme is involved in the local production of ET. ECE-2 produces mature ET-1 from Big ET-1, and bovine ECE-2 is a metalloprotease structurally related to ECE-1 and neutral endopeptidase. ECE-2 has been shown to convert endogenously synthesized Big ET-1 in the trans-Golgi apparatus [24]. The cell-to-cell communication pathways represented by the ET-1/ECE-1/ET_A axis and ET-3/ECE-1/ET_B axis are each involved in the development of distinct subsets of neural crest cell lineages. Epidermal melanocytes and enteric neurons of the distal gut were shown to be absent in embryos and reproduced the developmental phenotype in ET-3 and ET_BR in mice [24] (Figs. 1 and 2).

The immunohistochemical localization of ET has been reported in bone cells and vascular endothelial cells using the indirect immunogold method [25]. In metaphyseal bone marrow, strong staining was observed in osteoclasts, osteoblasts, young osteocytes, and endothelial cells. However, no immunoreactions were observed in bone, cartilage, matrices, or chondrocytes. Nakamura et al. [26] showed the presence of gold particles in the rough endoplasmic reticulum, Golgi apparatus, small vesicles, and lysosomes in cultured bovine endothelial cells by ET immunohistochemistry.

Elevated plasma ET-1 levels may be involved in the pathogenesis of cardiovascular diseases. The ET degradation enzyme consists of two subunits with molecular weights of 34 and 21 kDa, and the active enzyme complex with a molecular weight of 82 kDa and optimum pH of 5.5 has been purified. This enzyme plays a role in the homeostasis of ET-1 circulation and vascular tone [27]. A superfamily of zinc metalloproteases represented by ECE and neutral endopeptidase (EC 3.4.24.11) is involved in the metabolism of biologically active peptides, and membrane-bound metalloprotease as soluble secreted endopeptidase (SEP) hydrolyzes various vasoactive peptides including ET-1, ANP, and angiotensin. SEP activity was shown to be inhibited by phosphoramidon and neutral endopeptidase was only partially inhibited by the ECE-specific inhibitor FR90 1533 [28].

The ET receptor (ETR) is grouped into ET_A and ET_B, and these ETRs exist on blood vessels and non-vessel tissues. ET_AR is abun-

Please cite this article in press as: Tanaka S, et al. Signaling of endothelin involves bone and soft tissue remodeling by modulating wound healing and tumor progression. J Oral Maxillofac Surg Med Pathol (2016), http://dx.doi.org/10.1016/j.ajoms.2016.09.002