Endothelin Signaling in Bone

Jasmin Kristianto, PhD[a], Michael G. Johnson, PhD[b], Rafia Afzal, MBBS[c], Robert D. Blank, MD, PhD[a,d,*]

KEYWORDS

• WNT Signaling • Endothelin 1 signaling • Osteogenesis • Mechanotransduction • Micro-RNA

KEY POINTS

- The endothelin system includes 3 small peptide hormones that are secreted as inactive precursors, a pair of G-protein–coupled receptors, and a pair of membrane-bound, extracellular converting enzymes.
- Endothelin 1/endothelin receptor A signaling is essential for the development of the craniofacial skeleton. Knockouts of the *Edn1*, *Ednra*, and *Ece1* genes have lethal phenotypes.
- Endothelin signaling is osteogenic in the setting of prostate and breast cancer.
- Genetic evidence points to allelic variation of *Ece1* as a mediator of bone biomechanical performance.
- In vitro experiments indicate that ET signaling derepresses WNT signaling, and thus may function upstream of WNT in mediating mechanical homeostasis of skeletal mass.

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[a] Divisions of Endocrinology, Metabolism, and Clinical Nutrition, Department of Medicine, Medical College of Wisconsin, 9200 West Wisconsin Avenue, Milwaukee, WI 53226, USA; [b] Department of Medicine, University of Wisconsin, 600 Highland Avenue, Madison, WI 53792, USA; [c] Department of Anesthesiology, Aga Khan University Hospital, Stadium Road, Karachi 74800, Pakistan; [d] Medical Service, Clement J. Zablocki VAMC, 5000 West National Avenue, Milwaukee, WI 53295, USA
* Corresponding author. 9200 West Wisconsin Avenue, Milwaukee, WI 53226.
E-mail address: roblank@mcw.edu

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INTRODUCTION

Endothelin 1 (ET1; **Table 1** for gene and protein abbreviations) signaling has been recognized as a driver of osteoblastic metastasis for more than a decade and recent work points to its having a broader role in bone biology. This review first outlines the ET signaling pathway and ET metabolism. It next summarizes the role of ET1 signaling in craniofacial development. Then, it discusses observations relating ET signaling to osteoblastic and other osteosclerotic processes in cancer. Finally, it describes recent work in our laboratory that points to endothelin signaling as the role of an upstream mediator of WNT signaling, promoting bone matrix synthesis and mineralization. It concludes with a statement of some remaining gaps in knowledge and proposals for future research. These are informed by insights gained from study of ET signaling in the development and physiology of the cardiovascular system.

OVERVIEW OF THE ENDOTHELIN SIGNALING PATHWAY

The ET system includes 3 small peptide hormones,[1–3] ET1, ET2, and ET3; 2 G-protein–coupled receptors,[4,5] EDNRA and EDNRB; and 2 specific converting enzymes,[6,7] ECE1 and ECE2. The ETs are synthesized as prepropeptides that are first processed to biologically inactive, 37 to 41 amino acid propeptides, commonly known as "big ETs," by furinlike proteases before secretion.[8,9] After secretion, the big ETs must be converted to their active forms by proteolytic cleavage in the extracellular space. ECE1 and ECE2, which have different pH optima (neutral pH optimal for ECE1, acidic pH optimal for ECE2), catalyze ET activation by cleaving the big ETs to 21 amino acid active ETs. In addition, big ETs can be converted by a variety of other proteases (**Figs. 1** and **2**).[10–12]

The ET system was discovered in arteries, and it has since been shown that various elements of the system are expressed in a wide variety of tissues, but expression is not ubiquitous. Immortalized osteoblasts in culture express ET1, EDNRA, and ECE1, thus having the capacity for autocrine ET signaling within the lineage.[13] Conversely, ET2, ET3, EDNRB, and ECE2 are either not detected or expressed at very low levels in these cells.[13]

ENDOTHELIN 1 SIGNALING IN DEVELOPMENT

Knockout mice lacking either ET1 or EDNRA have very similar, lethal phenotypes that result from malformations of the craniofacial bones.[14,15] Mice die shortly after birth due to asphyxia, which can be overcome by tracheostomy. They have hypoplastic mandibles, homeotic transformation of the mandible to a maxillary morphology.[16,17]

Table 1
Gene and protein abbreviations

	Protein	Human Gene	Mouse Gene
Endothelin 1	ET1	*EDN1*	*Edn1*
Endothelin 2	ET2	*EDN2*	*Edn2*
Endothelin 3	ET3	*EDN3*	*Edn3*
Endothelin A-type receptor	EDNRA	*EDNRA*	*Ednra*
Endothelin B-type receptor	EDNRA	*EDNRB*	*Ednrb*
Endothelin converting enzyme 1	ECE1	*ECE1*	*Ece1*
Endothelin converting enzyme 2	ECE2	*ECE2*	*Ece2*