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Review

Matrix metalloproteinase-13: A special focus on its regulation by signaling cascades and microRNAs in bone

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ABSTRACT

Bone remodeling is an orchestrated process involving osteoblasts and osteoclasts to maintain mineral homeostasis in the internal milieu, mediated chiefly by matrix metalloproteinases (MMPs). MMP13, one amongst the MMPs plays a premier role in bone remodeling, and mutations in MMP13 have been implicated in various pathologies including cancer and arthritis. Transcriptional activation of MMP13 gene is tightly regulated by several signaling cascade components. Post-transcriptional regulators such as microRNAs (miRNAs) have also been shown to regulate MMP13 expression under physiological and pathological conditions. Hence, this review provides an outline of the structure of MMP13 gene and its regulation by signaling components, transcription factors and miRNAs in bone.

Contents

Abbreviations: AP-1, Activating protein-1; BMM cells, Bone marrow-derived monocyte cells; BMP2, Bone morphogenic protein 2; ECM, Extracellular matrix; FGF2, Fibroblast growth factor 2; GCTOB, Giant cell tumor of bone; GCTSCs, Giant cell tumor of bone stromal cells; HDAC4, Histone deacetalyse 4; IL-1β, Interleukin-1β; IVD, Intervertebral disc; LDD, Lumbar disc degeneration; MANDP1, Metaphyseal anadysplasia 1; MDST, Metaphyseal dysplasia, Spahr type; MEF2c, Myocyte enhancer factor 2C; miRNA, MicroRNA; MMP13, Matrix metalloproteinase-13; NP cells, Nucleus pulposus cells; OA, Osteoarthritis; OS, Osteosarcoma; PEA-3, Polyoma enhancer activator-3; PTH, Parathyroid hormone; RA, Rheumatoid arthritis; RD, Runt domain; RUNX2, Runt-related transcription factor 2; $SEMD_{MO}$, Spondyloepimetaphyseal dysplasia missouri variant; TGF-β1, Transforming growth factor-β1; TIMP, Tissue inhibitor of metalloproteinase; TNFα, Tumor necrosis factor α.

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1. Introduction

Bone is a mineralized connective tissue which provides support, locomotion, protection of soft tissues including calcium and phosphate storage. The tissue is majorly composed of osteoblasts, osteoclasts and osteocytes [1]. Bone is remodeled lifelong to ensure normal fracture healing and for maintaining mineral homeostasis [2,3]. The process is divided into the following phases: activation, resorption, reversal, formation, and termination. The process is mediated by bone-resorbing osteoclasts and bone-forming osteoblasts, arranged in anatomical structures called bone multicellular units (BMU) [4]. Extracellular matrix (ECM) is a three-dimensional structure encompassing collagens, glycoproteins, proteoglycans, mucins, elastic fibers, and growth factors, which cross-link to form a bioactive scaffold for bone tissue and plays an imperative role in bone repair [5]. Remodeling of the ECM is a complex process which needs to be tightly regulated as dysregulation can lead to pathological conditions and increase in disease progression [6]. Matrix metalloproteinases (MMPs) are a family of zinc-dependant enzymes which cleave components of the ECM [7]. MMPs are classified into collagenase, gelatinase, stromelysin, matrilysin, and membrane type MMP and others. Collagenases (MMP1, 8, 13) predominantly cleave interstitial collagens I, II and III. Gelatinases (MMP2, 9) breakdown gelatin and also target ECM molecules including type IV, V and XI collagen and elastin. Stromelysins (MMP3, −10, −11) are responsible for the degradation of fibronectin, elastin, collagen III, IV, V, IX and X. Matrilysins (MMP3, 26) act on lamin, fibronectin and collagen IV. Membrane type MMPs (MMP14, 15, 16, 17, 24) predominantly cleave fibronectin. Others such as MMP12 which rives fibronectin, elastin, and vitronectin, MMP20 which cleaves amelogenin, MMP23 which breaks down gelatin and MMP28 which cleaves casein have also been reported [8]. All these MMPs share a common structure which consists of a pro-domain followed by a catalytic region, hemopexin and a hinge region [7]. Among these MMPs, MMP13 is a collagenase-3 which plays a vital role in bone biology. It degrades not only collagen type II, but also collagens type I, III, and X which are essential components of the bone [6,9–11]. It is expressed by hypertrophic chondrocytes and osteoblasts during embryogenesis and in the adult bone during endochondral ossification [10]. Knockout models for 16 different MMPs have been studied to understand their importance in bone development [11]. MMP13 deficient mice showed impaired endochondral ossification as well as increased trabecular bone volume at skeletal maturity. MMP13 also plays a significant role in the regulation of human adipose tissue derived mesenchymal stem cells (hAT-MSC) towards osteoblast differentiation by polyphosphates [12]. Mutations in the MMP13 gene have been studied and linked to the occurrence of spondyloepimetaphyseal dysplasia [13–15]. The expression of MMP13 is tightly regulated in various bone cell types by a number of signaling components, transcription factors and other regulators such as microRNAs (miRNAs). miRNAs act as post-transcriptional regulators that negatively regulate gene expression and play a role in bone metabolism [16–18]. Thus, based on the importance of MMP13 function under normal physiological and pathological conditions, this review was focused on the genomic and protein structure of MMP13 and the regulation of its expression through various signaling cascades and transcription factors. Also, we highlighted the role of miRNA in MMP13 expression under pathological conditions.

2. Genome and protein structure of human MMP13

Human MMP13 gene comprised of 9 introns and 10 exons spanning 12, 500 bp on chromosome 11q22.3 [19] (Fig. 1). Transcriptional start site was mapped at 22 bp and 28 bp upstream from start codon ATG [19,20]. There were two major transcripts detected which was mainly due to occurrence of different polyadenylation sites [21,22]. The promoter region of human MMP13 gene is very complex in nature. It contains several consensus binding sites for transcription factors [20,23]. The major constituents of the promoter regions are TATA box region, AP-1 (activator protein-1), PEA-3 (polyoma enhancer activator 3) and RD (runt domain) sites in the proximal promoter region while AGRE (AG-rich element) is in the distal region of the promoter. The AP-1 site (TGACTCA) involves in the binding of the Fos and Jun family of proteins. This site promoted in the triggering of basal as well as induced transcription [20,23]. It was proven that AP-1 (−62/−55) located within 148 bp upstream to the rat MMP 13 gene transcriptional start site activates MMP13 transcription [24]. The human and rat MMP13 promoters have conserved transcription factor binding sites such as AP-1, p53, distal RD, AGRE and PEA-3 sites and the human MMP13 promoter region also varies with that of rat, as it lacks the sites such as AP-2, proximal RD, TRE like domains [24,25]. c-Fos and c-Jun proteins were shown to bind to the AP-1 site of the MMP13 promoter [26,27]. In human breast metastatic and invasive cells (MDA-MB231), ATF-3 interacted with Jun-B and c-Jun proteins forming a complex which bound to the AP-1 site, resulting in the transcription of MMP13 gene upon TGF-β1 treatment [28,29]. The RD site (TCTGCGGTC/TGACCGCAG) is also known as Cbfa1 (core binding factor 1) [30,31] or OSE2 (osteoblast specific element 2) [32] site where Runx2, a bone transcription factor binds [30–32]. The AP-1 proteins and Runx2 were shown to bind the AP-1 site and the RD site of the MMP13 promoter by PTH (parathyroid hormone)-treatment in osteoblastic cells [33]. Moreover, these proteins interacted with each other and promoted MMP13 expression in these cells [24]. Runx2 that binds to the RD site of the MMP13 promoter has been reported to undergo phosphorylation in response to PTH and TGF-β1-treatment in osteoblastic and non-osteoblastic cells [34,35]. The PEA-3 site (AGGAGA) is predominant towards binding of ETS-1 [36] family of oncoproteins. In some cells like chondrocytes, there was a co-operation between the proteins binding the AP-1 and PEA-3 sites [37,38], while Runx2 binds to the RD site [24,39]. The ETS region or PEA-3 site (−77/−71) with a core sequence of 5′-GGAA-3′ co-operated with the AP-1 site to regulate transcription of MMP13 gene [40]. The AGRE site, composed of two AAAAG half-sites separated by one base, or a repeat of the two GAAAA half-sites, (GAAAAGAAAAAG) acted towards the repression of the basal transcription of the MMP 13 gene [41]. The tantalizing fact is that the AGRE site was not found as such in the proximal promoter sequence of other human MMPs. The AGRE site, because of its unusual action of negative regulation and low abundance in gene promoter regions, has not yet been studied extensively.

Generally, MMPs are synthesized as pro-enzymes, and they must be processed by proteolytic cleavage at the N-terminus for