Archives of Biochemistry and Biophysics 561 (2014) 74–87

Contents lists available at ScienceDirect

Archives of Biochemistry and Biophysics

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

Review

Bone tissue remodeling and development: Focus on matrix metalloproteinase functions

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ARTICLE INFO

Article history:
Received 29 April 2014
and in revised form 17 July 2014
Available online 23 August 2014

Keywords:
Bone development
Bone remodeling
Extracellular Matrix
Matrix metalloproteinases
Tissue inhibitor of matrix metalloproteinases
RECK, Bone Bioengineering

ABSTRACT

Bone-forming cells originate from distinct embryological layers, mesoderm (axial and appendicular bones) and ectoderm (precursor of neural crest cells, which mainly form facial bones). These cells will develop bones by two principal mechanisms: intramembranous and endochondral ossification. In both cases, condensation of multipotent mesenchymal cells occurs, at the site of the future bone, which differentiate into bone and cartilage-forming cells. During long bone development, an initial cartilaginous template is formed and replaced by bone in a coordinated and refined program involving chondrocyte proliferation and maturation, vascular invasion, recruitment of adult stem cells and intense remodeling of cartilage and bone matrix. Matrix metalloproteinases (MMPs) are the most important enzymes for cleaving structural components of the extracellular matrix (ECM), as well as other non-ECM molecules in the ECM space, pericellular perimeter and intracellularly. Thus, the bioactive molecules generated act on several biological events, such as development, tissue remodeling and homeostasis. Since the discovery of collagenase in bone cells, more than half of the MMP members have been detected in bone tissues under both physiological and pathological conditions. Pivotal functions of MMPs during development and bone regeneration have been revealed by knockout mouse models, such as chondrocyte proliferation and differentiation, osteoclast recruitment and function, bone modeling, coupling of bone resorption and formation (bone remodeling), osteoblast recruitment and survival, angiogenesis, osteocyte viability and function (biomechanical properties); as such alterations in MMP function may alter bone quality. In this review, we look at the principal properties of MMPs and their inhibitors (TIMPs and RECK), provide an up-date on their known functions in bone development and remodeling and discuss their potential application to Bone Bioengineering.

Introduction

The extracellular matrix (ECM)[1] is constituted of structural molecules (proteins, proteoglycans, polysaccharides) and enzymes secreted by cells that form a tissue-specific tridimensional macromolecule network, creating the cellular microenvironment or niches [1,2]. Remodeling of the extracellular and pericellular environment by proteinases is finely regulated and profoundly affects cellular behaviors that are essential in many biological processes, such as maintenance of stem cell properties (stemness) and stem cell fate, embryonic development, morphogenesis, cell migration, cell differentiation, apoptosis and tissue remodeling [3]. When the regulation of ECM remodeling is lost, the integrity of tissues is compromised, making the microenvironment propitious for the initiation of

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[1] *Abbreviations used:* MMPs, matrix metalloproteinases; ECM, extracellular matrix; Ihh, Indian hedgehog; PTH, parathyroid hormone; PTHrP, parathyroid hormone–related protein; FGF, fibroblast growth factor; VEGF, vascular endothelial growth factor; CTGF, connective tissue growth factor; BMPs, bone morphogenetic proteins; BMUs, basic multicellular units; FGFRs, fibroblast growth factor receptors; YAP, Yes-association protein; PAT, palmitoyl acyltransferase; COMP, cartilage oligomeric matrix protein; MSCs, mesenchymal stem cells; AC, articular cartilage; BC, bone collar; BMC, bone marrow cavity; BS, bone spicules; BV, blood vessel; CB, cortical bone; Ch/C, chondroblast/chondrocyte; D, diaphysis; E, epiphyses; EL, epiphyseal line; Eo, endosteum; GP, growth plate; HZ, hypertrophic zone; M, metaphysis; MSC, mesenchymal stem cell; Ob, osteoblast; Oc, osteoclast; Oo, osteocyte; PC, proliferative chondrocyte; Pc, perichondrium; PHC, prehypertrophic chondrocyte; Po, periosteum; POC (COJ), primary ossification centres (chondro-osseous junction); PZ, proliferative zone; RZ, resting zone; TB, trabecular bone; SOC, secondary ossification centres; THC, terminal hypertrophic chondrocyte.

http://dx.doi.org/10.1016/j.abb.2014.07.034
0003-9861/

pathological processes, such as connective tissue diseases, cancer and metastasis (tumor microenvironment) [4,5].

Matrix metalloproteinases (MMPs) are the major enzyme family responsible for ECM remodeling and, collectively, they are able to cleave all ECM components by sharing common substrates. Traditionally, the biological role of MMPs has been associated only with ECM degradation and turnover. Recent studies in MMP gene-knockout animal models, degradomic and proteomic approaches have been important for changing the dogma concerning MMP function, showing overlapping functions (redundant and compensatory mechanisms), doubtful roles (protective or destructive), unexpected substrates and tissue-specific expression, depending on the biological process involved (proliferation, migration); thus, these enzymes regulate key cell behavior and signaling pathways [6–9]. Thus, the known specific proteolytic spectrum targets for these MMPs have been enlarged to include membrane surface proteins, non-ECM related pericellular molecules, other proteinases, intracellular substrates, proteinase inhibitors, chemotactic molecules, latent growth factors, protein-binding growth factors, membrane receptors, cell–cell and cell-ECM adhesion molecules. Accordingly, these enzymes are important for releasing molecules embedded within the ECM or membrane bound and to generate active biomolecules as products of ECM component cleavage (matrikins), which are crucial for physiological and pathological events, as extensively reviewed in the last decades [10–13].

Bone is a highly dynamic tissue and an important site of continuous tissue remodeling during development, homeostasis and tissue remodeling/repair. Embryologically, bone develops in two distinct manners: by intramembranous ossification (direct differentiation of mesenchymal cells into osteoblasts) or endochondral ossification (mesenchymal stem cells differentiated into chondrocytes that form a cartilaginous matrix template and are progressively replaced by bone matrix). Adult bone is continually remodeled throughout life by a physiological process, called bone remodeling or bone metabolism. Bone remodeling occurs via two coupled mechanisms named bone resorption and bone formation, coordinated by osteoclasts and osteoblasts, respectively. This process is also initiated after bone lesion or injury, leading to bone repair or bone regeneration by bone healing (tissue regeneration that recapitulates bone development without forming fibrous scars). Any imbalance between bone resorption and formation may lead to metabolic bone diseases, such as osteoporosis. Bone regeneration or bone repair depends on coordinated processes including ECM remodeling to form new tissue and to reestablish bone function. In all cases, correct ECM remodeling is required and MMPs appear to be essential.

Since the discovery of collagenolytic activity in rat bone cells [14], more than half of the members of the MMP family have been reported as active during osteogenesis and chondrogenesis in normal bone development in several mammalian species. These MMPs also contribute to skeletal pathologies involving cartilage and bone degradation, such as osteoporosis, rheumatoid arthritis, osteoarthritis, and other diseases [15–20]. Despite the expression of several MMPs in bone and cartilage cells during normal bone development, knockout mice models and human genetic diseases have been revealed the importance of the MMPs -2, -9, -13, -14, and -16 for skeletal development. It is now also recognized that the role of MMPs should be considered in a broader context than just for bone and cartilage matrix solubilization and should include other processes, such as chondrocyte proliferation and differentiation, osteoclast recruitment and function, bone modeling, coupling of bone resorption and formation (bone remodeling), osteoblast recruitment and survival, angiogenesis, and osteocyte viability and function (biomechanical properties).

In this review, we will look at the overall properties of MMPs and their inhibitors (TIMPs and RECK), provide an up-date on their functions in bone development and remodeling and discuss their potential applications in Bone Bioengineering.

Overview of the general properties of matrix metalloproteinases (MMPs)

The first MMP (collagenase) was identified in tadpole tails during metamorphosis in 1962 by Gross and Lapière [21]. Most MMPs have been studied in vertebrates (25 members), but are also found in lower animals and plants. In humans, the MMPs comprise 24 genes, encoding 23 proteins, as one MMP (MMP-23) is coded by two identical genes at chromosome 1 (MMP-23A and MMP-23B). Mammalian MMPs are classified according to; (I) their localization, soluble (secreted into ECM) or insoluble (anchored on cell membrane); (II) their similarities in tridimensional structure and substrate affinity, being usually divided into six subgroups: collagenases (MMPs -1, -8, and -13), gelatinases (MMPs -2 and -9), stromelysins (MMPs -3, -10 and -11), matrilysins (MMPs -7 and -26), membrane-type metalloproteinase (MMPs -14, -15, -16, -17, and -24 or MMP-MT1, MT2, MT3, MT4, MT5 and MT6, respectively), and others (MMPs -12, -18, -19, -20, -21, -22, -23, -27, and -28); and (III) numerically listed according to chronological discovery. MMPs -4, -5 and -6 are missing in the list since they were shown to be identical to other members of the family [22] (Fig. 1).

The regulation of MMPs occurs at multiple levels, according to the cell type involved, in a temporal and spatial manner and quantities, by intra and extracellular mechanisms. Inductive or suppressive signaling from the ECM (cytokines, growth factors, EMMPRIN, signals from integrins, ECM proteins, cellular stress, morphological changes, etc) and intracellular signal transduction induce the activation or repression of the MMP genes. In the nucleus, these genes may be transcriptionally controlled by genetic alterations (polymorphisms or mutations, particularly in promoter regions of the MMP genes) and by epigenetic control (DNA methylation status and remodeling of chromatin by histone acetylation) as well as post-transcriptionally through mRNA processing. In the cytoplasm, MMPs may be regulated post-transcriptionally by mRNA stability (microRNAs action and degradation pathway), intracellular activation of furin susceptible MMPs, insertion of prosthetic groups (*N* and *O*-glycosylation and GPI-anchor) or specific domains in the pro-MMP structure, and, finally, by inducible and constitutive pro-enzyme secretion into the ECM. Certain MMPs may be stored in the cytoplasm within granules in specific cell types prior to stimuli, such as inflammatory stimuli, and then secreted. MMPs on the cellular membrane may be regulated by their localization on specialized membrane microdomains (lipid rafts or caveolae), by endocytosis/recycling (clathrin or caveolin-dependent) and intracellular degradation. In the ECM, the MMPs may be controlled by proteolytic processing and inactivation, proteolytic activation of pro-MMPs, binding of pro and active forms to inhibitors, and interaction with specific ECM components, leading to specific localization (pericellular perimeter or distant from cell secretion point within ECM), and allosteric control [23–33].

The balance between MMPs and their inhibitors is required for physiological ECM remodeling and imbalance in these enzymes leads to pathological states. In the tissues, MMPs are mainly reversibly inhibited in the ECM by their physiologic tissue inhibitors (TIMPs), while the cell surface MMPs are inhibited by the RECK glycoprotein [34] (Fig. 1).

Overview of the principal cellular and molecular aspects of bone development and remodeling

The mammalian skeleton has three different embryological origins: (I) paraxial mesoderm, which gives rise to the axial skeleton;