Microbe-Associated Bone Cell Differentiation

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Gut microbiota has emerged as an important regulator of bone homeostasis. In particular, the modulation of innate immunity and bone homeostasis is mediated through the interaction between microbe-associated molecular patterns (MAMPs) and the host pattern recognition receptors including Toll-like receptors and nucleotide-binding oligomerization domains. Pathogenic bacteria such as Porphyromonas gingivalis and Staphylococcus aureus tend to induce bone destruction and cause various inflammatory bone diseases including periodontal diseases, osteomyelitis, and septic arthritis. On the other hand, probiotic bacteria such as Lactobacillus and Bifidobacterium species can prevent bone loss. In addition, bacterial metabolites and various secretory molecules such as short chain fatty acids and cyclic nucleotides can also affect bone homeostasis.

Keywords: bone diseases ; bone homeostasis ; bacteria ; microbe-associated molecular patterns ; osteoblast ; osteoclast ; pattern-recognition receptors ; secretory microbial molecules

1. Introduction

The bone remodeling process is regulated by representative bone cells known as osteoclasts and osteoblasts [1]. The balance between bone-resorbing osteoclasts and bone-forming osteoblasts is essential for maintaining bone homeostasis [2]. However, imbalance between bone resorption and formation could lead to bone diseases [3]. Excessive osteoclast activity causes various bone diseases including osteoporosis, septic arthritis, osteomyelitis, and alveolar bone loss in periodontal diseases [4][5][6]. Especially, bacterial infections can directly affect bone homeostasis by increasing osteoclast differentiation and activation and/or decreasing osteoblast differentiation and activation [7]. For example, *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Neisseria gonorrhoeae* are commonly found in patients with septic arthritis, resulting in cartilage and bone destruction within the joint [8]. *Staphylococcus* species such as *S. aureus* and *Staphylococcus epidermidis* are etiological agents of osteomyelitis [5]. Major oral pathogens, including *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, are associated with periodontal diseases, manifesting alveolar bone loss [9]. However, unlike those pathogens, probiotics which are microorganisms that offer health benefits to the hosts are known to increase mineral density and volume of the bone [10]. For instance, *Lactobacillus reuteri* and *Lactobacillus rhamnosus* GG upregulate bone volume of mice [11][12]. In addition, other probiotics such as *Lactobacillus gasseri* and *Lactobacillus brevis* reduce bone loss and inflammation in mouse periodontitis model [13][14].

Bacteria have unique structural components called microbe-associated molecular patterns (MAMPs) including lipopolysaccharide (LPS), lipoteichoic acid (LTA), lipoprotein (LPP), and peptidoglycan (PGN) [15]. The recognition of MAMPs by pattern recognition receptors (PRRs) is crucial for inducing host immune responses [15]. In addition, secretory microbial molecules including short chain fatty acid (SCFA), extracellular vesicle (EV), extracellular polysaccharide, and cyclic dinucleotide (CDN) also modulate bone cells [16][17][18]. Therefore, for a clear understanding of the regulation of bone metabolism by bacteria, it is essential to understand the effects of MAMPs and secretory microbial molecules on bone cells and their regulatory mechanism.

2. Microbe-Associated Molecular Patterns

MAMPs are structural or secretory molecules that are highly conserved in most microbes [19]. Well-known MAMPs are bacterial polysaccharides (LPS and LTA), surface proteins (LPP and adhesin), PGNs, and secretory molecules (SCFA, EV, extracellular polysaccharide, and CDN) [20]. These MAMPs can be sensed by various host PRRs, such as Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), or G-protein coupled receptors (GPCRs) [21][22]. Indeed, there are many host PRRs classified according to their location, function, and ligand specificity [23]. There are typically four types of PRRs: TLRs, NLRs, C-type lectin receptors, and RIG-1 like receptors [21]. Among these, TLRs localized at plasma membrane or in endosomes and NLRs localized in cytoplasm are the major PRRs in recognizing bacterial MAMPs [21]. For instance, TLR4 senses LPS, and TLR2 senses LPP and LTA [24]. On the

other hand, NOD1 and NOD2 recognize bacterial PGNs through their distinct structural moieties, d-glutamyl-*meso*-diaminopimelic acid (iE-DAP) and muramyl dipeptide (MDP), respectively [25]. Based on their displayed patterns, each host receptor responds to its specific bacterial ligand, subsequently producing anti- or pro-inflammatory cytokines and chemokines to counteract against invading microbes [26]. It has been reported that pathogens or probiotics and their MAMPs could also affect osteoimmunological responses (Table 1) [27]. Therefore, we will focus on MAMPs and their effects on bone homeostasis in this section.

Table 1. Effects of cell wall components on bone metabolism.

MAMPs	Receptor	Effects	References
Lipopolysaccharide	TLR4	Inducing bone loss Inhibiting osteoclastogenesis on macrophages Facilitating osteoclast differentiation on committed osteoclasts Downregulating osteoblast differentiation	[28][29][30][31][32][33][34][35]
Lipoteichoic acid	TLR2	Healing femoral fractures in mice Attenuating osteoclast differentiation and activating phagocytosis Upregulating osteogenic markers and osteoblastogenesis	[36][37][38][39][40]
Lipoprotein	TLR2	Promoting bone resorption Upregulating osteoclast differentiation Stimulating osteoblasts to elevate RANKL/OPG ratio	[41][42][43]
Fimbria	TLR4	Inducing osteoclastogenesis and bone resorption	[44][45][46][47][48][49]
Peptidoglycan	NOD1	Enhancing osteoclastogenesis and bone resorption Triggering osteoclast differentiation synergistically with LPS	[50][51][52][53][54][55][56]
	NOD2	Upregulation of bone density Facilitating osteoblast differentiation Diminishing osteoclastogenesis by reducing RANKL/OPG ratio	[54][57]

3. Therapeutics

Microbes influence bone metabolism by constant interaction with host using their various MAMPs (Table 2) [7]. In infectious condition, MAMPs often trigger immoderate osteoclastogenesis or inhibit osteoblast differentiation through the activation of immune responses, causing bone diseases such as osteomyelitis, osteoporosis, and periodontitis [7]. Antibiotics are commonly used to treat MAMP-induced bone diseases in bacterial infection [58]. Nevertheless, the emergence of antibiotic-resistant bacteria and remaining MAMPs after treatment pose significant challenge for complete clearance [59]. Therefore, further studies are needed to understand the role of MAMPs in bone diseases and to control the immune responses induced by MAMPs.

Table 2. Effects of secretory microbial molecules on bone metabolism.

MAMPs	Mechanism	Effects on Bone Metabolism	References
Short chain fatty acids	Activation of GPCRs Inhibition of histone deacetylases	Inhibited osteoclast differentiation and function Upregulated osteogenic factors in low dose Attenuated osteoblast differentiation and mineralization Prevented bone loss in various mouse models	[60][61][62][63]
Extracellular vesicles	Activation of TLR2 Induction of pro-inflammatory cytokines	Downregulated osteoblast differentiation and activity Regulated RANKL and OPG expression in mesenchymal cells	[17]
Extracellular polysaccharides	Activation of TLR2	Inhibited osteoclast differentiation from macrophages, but some EPS increased collagenolytic activity of osteoclasts Enhanced osteoblast differentiation, but oral pathogen-derived CPS decreased proliferation of osteoblasts	[64][65][66][67]
Cyclic dinucleotides	Induction of STING-mediated IFN-β	Inhibited differentiation of macropahges into mature osteoclasts Alleviated RANKL-induced bone destruction	[18]

On the other hand, several studies investigated that some MAMPs, especially derived from probiotics, decrease bone resorption or enhance bone formation by controlling the differentiation of osteoclasts or osteoblasts, respectively, in both in vitro and in vivo studies [18][57][63]. Many therapeutic drugs, such as bisphosphonates, monoclonal antibodies, or hormone preparations, are traditionally developed to treat bone diseases by inhibiting bone resorption or inducing bone formation [68][69][70]. However, conventional drugs show unexpected side effects, such as nausea or osteonecrosis of jaw [70][71][72]. Therefore, we suggest that probiotic-derived MAMPs could alternatively be used in place of conventional therapies. To evaluate their therapeutic use, we have discussed below how to treat MAMP-induced bone diseases and how to exploit MAMPs in bone health.

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