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Exercise, Interleukins, and Bone Homeostasis

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ABSTRACT

The proper balance between the production of osteoclastogenic and anti-osteoclastogenic interleukins by immune and bone cells is critical for the preservation of bone homeostasis and the maintenance of optimal bone mass. This article summarizes the mechanisms whereby interleukins with osteoclastogenic properties (interleukin-1 β , interleukin 17A, interferon- γ , and tumor necrosis factor- α) and anti-osteoclastogenic properties (interleukin-1 receptor antagonist, interleukin 4, interleukin-6, interleukin-10, interleukin 13, and transforming factor- β) effect the activities of osteoblasts, osteoclasts and osteocytes. It points out that long term moderate intensity aerobic exercise training can provide a cost-effective means for achieving a proper balance between immune cells producing osteoclastogenic and anti-osteoclastogenic interleukins.

INTRODUCTION

Interest in cytokines as regulators of bone metabolism began with the experiments of Horton and associates who, in 1972, found that conditioned medium from phytohemagglutinin (PHA)-stimulated peripheral blood mononuclear cells contained bone resorbing (osteoclastogenic) activity [1]. This activity was eventually found to be due to interleukin (IL)-1 and tumor necrosis factor (TNF)- α [2,3], prompting a series of studies examining the role of these and other pro-inflammatory cytokines as mediators of bone resorption in periodontal disease, rheumatoid arthritis, osteolytic malignancies, and osteoporosis [4-9]. In addition to IL-1 and TNF- α , the spectrum of cytokines with osteoclastogenic effects has expanded to include IL-17A [10]. In blood, these cytokines are variably produced by T helper type 1 (Th1) cells, natural killer (NK) cells, Th1-derived CD8⁺ T cells, Th17 cells, and M1-polarized macrophages [11,12].

Subsequent studies have identified several interleukins whose activities inhibit bone resorption and/or promote bone formation (anti-osteoclastogenic cytokines). These include IL-1 receptor antagonist (IL-1Ra), IL-4, IL-10, IL-13 and transforming growth factor (TGF)- β [10,13]. In blood, these cytokines are variably produced by Th2 cells, T and B regulatory cells, T follicular helper (T_{FH}) cells, M2-polarized macrophages, and T2-derived CD8⁺ T cells [10-13].

There are several pleiotropic cytokines, interferon (IFN)- λ and IL-6, whose effects on bone varies depending on experimental conditions; however, in most circumstances IL-6 is anti-osteogenic whereas IFN- λ is osteoclastogenic [14]. In blood, IFN- λ is produced by Th1 cells and M1-polarized macrophages, whereas IL-6 is produced primarily by macrophages [10-13].

Immune cells occupying the microenvironment of bone are ideally situated to influence the ontogeny and functioning of cells responsible for bone formation (osteoblasts), bone resorption

(osteoclasts), and the transduction of bone loading signals (osteocytes) [14]. Osteoblasts and osteoclasts are derived from bone marrow stromal mononuclear cells, and retain the capacity to produce several cytokines, particularly IL-6 and TGF- β . Osteocytes are derived from osteoblasts as they age and become imbedded in the lacuno-canalicular network of bone [15].

Mechanism of action.

Osteoclastogenic interleukins

IL-1 α and TNF- α promote osteoclastogenesis by inducing osteoblasts to express receptor activator of nuclear factor kappa B (NF κ B) ligand (RANKL) and bind to RANKL receptors (RANK) on stromal osteoclast precursors, or produce soluble RANKL to perform the same function [5,8]. TNF- α potently activates osteoclasts through a direct action independent of and strongly synergistic with RANKL [16]; it also inhibits bone formation in vitro [17]. IL-1 α and TNF- α exert potent anti-apoptotic effects on osteoclasts [10], and interact synergistically with one another [18] and with PTH 19] to enhance their bone resorptive capacities.

IL-17A induces RANKL expression in osteoblasts, promoting the differentiation of osteoclasts from their stromal mononuclear cell precursors. This cytokine has the capacity to activate macrophages to secrete IL-1 β and TNF- α , thereby indirectly upregulating osteoclastogenesis. In rodents, neutralization of IL-17A with polyclonal anti-17A antibody has been shown to downregulate bone erosion, RANKL expression, and the number of RANKL positive cells in inflamed joints [10].

IFN- λ effects on bone metabolism varies depending on experimental conditions [20]. It inhibits RANKL- induced osteoclastogenesis by degrading the RANK adapter protein TRAF6 (tumor necrosis factor receptor-associated factor 6), a mechanism felt to protect against excessive

T cell-mediated bone resorption [21]. Recombinant IFN- λ has also been shown to preferentially inhibit IL-1 and TNF-stimulated bone resorption in vitro [22], and to be osteoprotective when administered to ovariectomized mice [23]. In contrast, this cytokine has been shown to inhibit collagen synthesis in cultures of rat [24] and human bone cells [25], to cause bone loss when administered intra-peritoneally to experimental rats [26], and to demonstrate efficacy in the treatment of osteopetrosis [27]. IFN- λ also promotes osteoclastogenesis indirectly by upregulating MHC class I and II expression on antigen presenting cells and by stimulating the release of TNF- α and RANKL by activated T cells [20]. The evidence suggests that under conditions of estrogen deficiency, infection, and/or inflammation, the net effect of IFN- λ is biased toward bone resorption [20]. Of note is that under physiologic conditions secretion of this cytokine is strictly confined to sites of cell-to-cell interaction between immune cells where it is rapidly destroyed, and thus its potential to function in free form is limited.

Anti-osteoclastogenic cytokines

IL-1Ra, by binding to type I and II IL-1 receptors, inhibits IL-1-mediated osteoclastogenesis [13].

IL-4 and IL-13 represses osteoclast development and function by a STAT6-dependent inhibition of RANKL [28]. They also upregulate osteoblast production of osteoprotegerin (OPG), a decoy RANKL receptor and potent inhibitor of osteoclastogenesis [29]. IL-4 has the potential to protect bone indirectly by promoting the differentiation of Th2 cells and M2-polarized macrophages and by inhibiting the differentiation of Th1 cells from activated CD4⁺ T cells; it also inhibits secretion of IL-1 β and TNF- α by human monocytes [30].

IL-10 is a potent inhibitor of bone resorption; it inhibits RANKL-mediated

osteoclastogenesis by downregulating NFATc1 (nuclear factor of activated T cells) expression and nuclear translocation in mononuclear osteoclast precursors, and upregulates the expression of osteoprotegerin [31]. IL-10 protects bone indirectly by suppressing the secretion of osteoclastogenic cytokines in immune cells, most notably in activated M1-polarized macrophages [32]; it also inhibits lymphocyte production of IFN- λ [33]. IL-10 deficient mice develop osteopenia, decreased bone formation, and mechanical fragility of long bones [34], attesting to the importance of its anti-resorptive effects in vivo.

TGF- β has pleiotropic effects on bone, which are predominantly osteogenic. By decreasing RANKL expression and enhancing OPG production in osteoblasts, this cytokine inhibits the proliferation, differentiation, and fusion of osteoclast precursors, inhibits osteoclast activity, and counteracts the resorptive activities of IL-1 and TNF- α [35-38]. TGF- β is a potent stimulator of bone formation, prompting osteoblast differentiation and synthesis of osteoid matrix and inhibiting the activity of osteoid degrading enzymes [38]; it also modulates osteoblast responses to osteotropic hormones, and serves as a chemotactic agent for cells of the osteoblast phenotype [35]. A latent form of TGF- β is found in high concentrations in the matrix of calcified bone; when released in active form by the resorptive action of osteoclasts this cytokine is thought to help initiate the transition (coupling) phase of bone remodeling by stimulating osteoblast differentiation and recruitment and by suppressing osteoclastogenesis and osteoclast-mediated resorption [9,35-38]. Evidence suggests that TGF- β couples bone resorption to bone formation by binding to receptors on osteoclasts and inducing the secretion of Wnt1, a protein crucial to normal bone formation [39]. TGF- β can also protect bone indirectly by inhibiting the expression of proinflammatory cytokines and repressing IFN- λ production by immune cells [9,11].

IL-6 exerts context-dependent effects on bone metabolism [5,40,41]. Although it can stimulate osteoclastogenesis and bone resorption by upregulating RANKL expression in osteoblasts [42], its effects on bone metabolism are predominantly osteogenic and anti-resorptive. IL-6 enhances bone formation by promoting the differentiation of osteoblast precursors [43,44] and by protecting osteoblasts against apoptosis [5,45]; it can inhibit bone resorption directly by downregulating RANKL signaling pathways in osteoclasts [46] and indirectly by suppressing the production of TNF- α and IL-1 and stimulating the production of IL-4, IL-10 and IL-1Ra by immune cells [47]. It is also an essential growth factor for B cells, the primary source of OPG in bone marrow stroma [48], and can induce IL-2 production in T cells [49]. IL-6 is produced in osteoblasts and osteocytes in response to bone loading signals, and, like TGF- β , plays an important role in bone remodeling [50,51].

Effect of Exercise

In a clinical study involving 43 adult subjects, we found that 6 months of moderate intensity exercise decreased the spontaneous and PHA-induced production of osteoclastogenic cytokines (IL-1, TNF- α , and IFN- γ) in cultured peripheral blood mononuclear cells (PBMCs) by 24% and 59%, respectively. In contrast, the exercise training program increased the spontaneous and PHA-induced production of anti-osteoclastogenic cytokines (IL-4, IL-6, IL-10, and TGF- β) by 89% and 50%, respectively. This change was accompanied by a 16% reduction in plasma levels of C-terminal telopeptides of Type I collagen, a reliable marker of bone resorption, and an 9.8% increase in plasma levels of osteocalcin, a reliable marker of bone formation. The reduction in bone resorption was proportionate to the time subjects spent in each training session doing aerobic exercises (75 minutes on average) [14]. Thus, one of the mechanisms whereby sustained exercise training enhances bone

health is by favorably changing the balance between PBMCs producing osteoclastogenic and anti-osteoclastogenic cytokines. The mechanism(s) responsible for these changes is currently under investigation.

Conclusion

The proper balance between the production of osteoclastogenic and anti-osteoclastogenic interleukins by immune and bone cells is critical for the preservation of bone homeostasis and the maintenance of optimal bone mass. Long term moderate intensity aerobic exercise training provides a cost-effective means for achieving this goal.

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