Review

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Mechanism of Interleukin-17A Regulation of Mesenchymal Stroma/Stem Cell Osteogenic Differentiation

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The immune and musculoskeletal systems closely interplay in bone repair and regeneration. After bone injury, the body produces high levels of cytokines and signaling molecules to balance bone formation and resorption. Interleukin (IL)-17A, a cytokine expressed early in the inflammatory process, profoundly influences osteoprogenitor cell fate, thereby contributing to bone homeostasis. In addition, mesenchymal stromal/stem cells (MSCs) can differentiate into osteoblasts, contributing to bone repair and regeneration. Although IL-17A can influence MSCs to become early osteoprogenitor cells, it also can inhibit bone formation. However, the reasons for these dual roles are not yet fully understood. This review overviews IL-17A signaling and the mechanisms that govern MSCs' osteogenic differentiation and summarizes relevant data from the literature on IL-17A's pro- and anti-osteogenic roles.

Keywords: IL-17A; mesenchymal stem cells; osteoblast; bone; osteogenesis; inflammation

Introduction

Mesenchymal stromal/stem cells (MSCs) undergo a remarkable transformation to osteoblasts through the intricate process of osteogenesis. This process involves numerous molecular and cellular interactions that guide the differentiation of MSCs into osteoblasts, ultimately contributing to the generation of strong and healthy bones [1,2]. MSCs are characterized by their capacity for differentiation towards mesodermal lineages, including osteoblastogenesis [3,4]. Disbalance of the inflammatory response may lead to compromised fibrous wrapping and skeletal attachment, influencing bone tissue repair and regeneration. However, chemokines and cytokines generated during inflammatory cascades can actively facilitate mesenchymal stem cells' differentiation into osteogenic lineages. Contrary to previous beliefs, which emphasized the necessity of inflammation inhibition for optimal bone formation, current understanding indicates that a well-modulated inflammatory milieu is indispensable for achieving proper bone healing [5,6]. Bone trauma inevitably results in inflammation, and the inflammatory response is believed to be essential for bone healing and regeneration. In this sense, studies have shown that many inflammatory diseases are closely related to the bone immune system [7,8].

The immune system's interaction with the musculoskeletal system was first demonstrated in the 1970s. During bone injury, an increase in cytokines due to the inflammatory milieu seems to stimulate osteoclastogenesis associated with bone reabsorption, giving rise to a new area of investigation named osteoimmunology and providing new potential therapeutic targets for bone disorders [9,10]. Interleukin (IL-17)A, a proinflammatory cytokine vital in host infection defense, has been demonstrated to participate in autoimmune and inflammation-associated pathologies and bone physiopathology [11].

This review examines the signaling pathways of IL-17A and the mechanisms that regulate the osteogenic differentiation of MSCs. While IL-17A has been shown to promote the formation of osteoblasts, its effects can vary depending on the target cells and tissue context, leading to inconsistent findings. This review presents findings that support both the promotive and inhibitory effects of IL-17A on osteogenesis, providing insights into its significance in bone repair and regeneration.

Mesenchymal Stromal/Stem Cells and Bone Tissue

MSCs were first identified as bone marrow (BM) stroma cells (BMMSCs) and characterized by their ability to facilitate hematopoiesis after being transplanted into nude mice [12,13]. Currently, MSCs must meet specific criteria for identification and characterization. The Interna-

tional Society for Cellular Therapy (ISCT) has established minimum standards for MSC characterization requiring the cells to have a fibroblast-like appearance, adhere to plastic, and differentiate into adipocytes, osteocytes, and chondrocytes. Furthermore, MSCs should be more than 95% positive for cluster of differentiation (CD)73, CD90, and CD105 markers while being negative or no more than 2% positive for leukocyte markers such as CD45, CD34, CD14, CD11b, and CD19 or human leukocyte antigen—DR isotype (HLA-DR) [14–17].

BM, fatty, and dental tissues are commonly used sources for basic research and clinical applications [18]. Unlike embryonic MSCs, using adult MSCs raises no biological or ethical concerns, and they can be used as autologous transplants, providing new bioengineering and cell-based clinical applications [19–23].

MSCs can evade immune-system recognition, making them a promising tool in clinical applications. MSCs exhibit hypoimmunogenic features because they express low levels of the class I major histocompatibility complex (MHC) molecules responsible for identifying foreign cells and initiating an immune response. MSCs do not express class II MHC or the costimulatory proteins CD40, CD80, and CD86 necessary for stimulating an immune response. Therefore, MSCs can avoid detection by the immune system, making them an attractive option for cellular therapies [24,25]. Moreover, MSCs exhibit remarkable antimicrobial properties, and immunomodulatory, immunosuppressive, and anti-inflammatory features. Therefore, MSCs are good candidates for study and possible use in bone-regeneration and healing therapies [26–29].

As a supportive skeleton, bone contributes to the locomotion and protection of soft tissues and vital organs while regulating blood pH and maintaining Ca^{2+} and PO_4^{3-} levels [30–32]. Bone tissue consists of two main compartments: (i) connective bone tissue, rich in extracellular matrix (ECM) and containing abundant organic collagen (COL) fibers (~90% of proteins) and hydroxyapatite [32–35]; and (ii) a cellular compartment comprising bone osteoprogenitors, osteoblasts, osteocytes, and osteoclasts [34,36,37].

Bone tissue is created step by step, beginning with the recruitment of MSCs from the periosteum to areas where the bone is being remodeled, followed by the multiplication of cells and then their commitment to a particular lineage [38]. Initially, MSCs begin differentiation towards highly proliferating pre-osteoblasts that do not yet generate an ECM. These cells then stop proliferating and begin expressing and secreting type I collagen, proteoglycans, and non-collagen proteins. Phosphate is also released by phosphatases associated with osteoblasts, leading to a mineralization process that involves binding calcium and phosphates to generate hydroxyapatite. Osteoblasts then undergo differentiation into osteocytes, which are embedded within lacunae as long-lived cells with an average half-life of approximately 25 years. They comprise 90–95% of bone cells and are crucial in regulating bone homeostasis, sensing inorganic molecules, and maintaining bone tissue functionality [38–46]. Meanwhile, during embryonic development, bones grow in length through endochondral ossification, a process in which bone gradually replaces cartilage to increase the bone's ability to withstand compression [47,48].

Bone homeostasis is a dynamic equilibrium of resorption and bone production in which osteoblasts/osteocytes and osteoclasts actively participate in constant bone fine-tuning [43,44]. In the meantime, impaired cell differentiation can cause bone pathologies such as osteoporosis due to an imbalance in BMMSCs differentiation towards adipocytes rather than osteoblast/osteocyte generation [49,50].

From the molecular point of view, early osteogenesis involves hedgehog proteins, bone morphogenetic proteins (BMPs), endocrine hormones, epigenetic modulators, cytokines, growth factor expression, and the Wingless-related integration site (Wnt)/β-catenin intracellular transduction pathway, which actively regulates osteoblast fate [49,51]. For instance, Runt-related transcription factor 2 (RUNX2)/core-binding factor subunit alpha-1 and its effector osterix (OSX) play a vital role in the osteogenesis process; both RUNX2 and OSX control bone mineralization and MSC differentiation [52,53]. Early osteoblast differentiation implicates RUNX2 expression and function; then, its expression decreases during late osteoblastogenesis, while OSX and β-catenin are upregulated, thus promoting osteoblast maturation [49,51–53]. RUNX2's molecular structure encompasses a runt DNA-binding domain and controls the expression of genes encoding collagen-type 1 (*COL1*), osteocalcin (*OCN*), and osteopontin (*OPN*), thus contributing to bone ECM production [54–56]. At the same time, more advanced stages of osteoblast differentiation involve the expression of *COL1*, osteoprotegerin (*OPG*), and osteonectin, with *OCN* and *OPN* essentially expressed at the end of osteogenesis differentiation [51,57–59]. OPG acts as a soluble decoy receptor of nuclear factor (NF)-κB-ligand (RANKL), inhibiting osteoclastogenesis and excessive bone resorption [60–62]. Osteonectin initiates mineralization, OCN inhibits bone resorption, and OPN controls bone generation and conservation [63–65].

Furthermore, Wnt/β-catenin, BMPs, transforming growth factor (TGF)-β1, hedgehog (HH), and Nel-like protein type 1 (NELL-1) induce RUNX2 expression and activity. The Wnt/β-catenin canonical pathway regulates MSC commitment to the osteoblastic lineage by inducing RUNX2, distal-less homeobox 5 (Dlx5), and OSX, promoting MSC progression into mature osteoblasts [42,66–70]. BMP induces MSC differentiation towards the osteochondral lineage and regulates postnatal bone and cartilage maintenance [71,72]. Moreover, BMP signaling in primary BMMSCs promotes Dlx2 and Dlx5 expression that subsequently induces RUNX2, OSX, and osteoactivin ex-

pression, among others, which stimulate bone formation [73,74]. Additionally, while osteoblastogenesis occurs, Smad6 can inhibit BMP signaling and RUNX2 expression, acting as a negative regulatory feedback loop [72,75].

Interleukin-17A

Historically, IL-17A was discovered as cytotoxic T lymphocyte antigen 8 (CTLA8) in 1993, and in 1995, it was found to share a sequence homology of about 57% with herpes virus saimiri gene 13 (HVS13). Both factors increase lymphocyte T-cell propagation via binding to specific cell-surface receptors; thus, they are named IL-17, viral(v) IL-17, and the IL-17 receptor (IL-17R), correspondingly [76,77]. Afterward, by studying T helper (Th)-cell differentiation, a Th-cell subtype was discovered that could produce IL-17A and was thus named the Th17 cell [78,79]. Th17 cells produce IL-17A and IL-17F to aid in host defense against bacterial and fungal infection and recruit neutrophils to infected tissues [80–82]. Dysfunction in Th17 regulation can exacerbate the pathogenesis of inflammatory and autoimmune conditions, including psoriasis, ulcerative colitis or Crohn's disease, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and cancer [11,79,83,84].

The IL-17 family comprises six structurally related glycosylated factors (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F) found via gene-screening. These factors have molecular weights of approximately 20–30 kDa and share 20–50% sequence homology with IL-17A [85,86]. IL-17 cytokines bind the IL-17 receptor (R) family at the cell surface, comprising IL-17RA, -RB, -RC, -RD, and -RE [80,83,87,88]. The initiation of signaling by IL-17A occurs through its binding to a receptor complex comprised of IL-17RA and IL-17RC, activating the multifunctional adaptor nuclear factor (NF)-κB activator 1 (Act1) that interacts with IL-17R via the SEF/IL-17 receptor (SEFIR) domain. Downstream intracellular signaling is then activated through interaction between the tumor necrosis factor (TNF) receptor-associated factor (TRAF)6 complex and Act1, involving NF-κB and mitogen-activated protein kinases (extracellular signal-regulated kinase (ERK)1,2, p38, and Jun N-terminal kinase (JNK)). Additionally, the activated IL-17/IL-17R/Act1 complex can signal through the TRAF4/mitogen-activated protein kinase kinase kinase (MEKK)3/mitogen-activated protein kinase kinase (MEK)5/ERK5 axis. Noncanonical signaling pathways of IL-17A include the TRAF2/5–human antigen R (HuR)–alternative splicing factor (ASF) axis, controlling inflammatory cytokines' mRNA stability and chemokine genes responsive to IL-17A (Fig. 1) [80,88–90].

Interleukin-17A's Effect on MSC Osteogenic Differentiation

IL-17A signaling influences the connection between the immune and musculoskeletal systems, which is crucial for maintaining bone homeostasis [91,92]. Inflammation, in particular, plays a vital role in bone health and turnover, impacting conditions like bone fracture healing, arthritis, osteoarthritis (OA), SLE, RA, and systemic sclerosis (SSc) [91,93].

Various innate and adaptive immune cells infiltrate damaged sites during bone repair and regeneration and control bone generation [94]. While cytokines like IL-6, TNF-α, and IL-17A play a significant role in bone healing and regeneration, they can also over-enhance inflammation, leading to abnormal bone repair and inflammatory musculoskeletal disorders [91].

IL-17A also regulates the proliferation, migration, and differentiation of MSCs, which are crucial for bone regeneration and homeostasis. MSCs express high levels of IL-17RA and other IL-17-receptor family members [95]. For instance, in murine BM-derived MSCs, IL-17A increases the frequency and size of colony-forming units-fibroblasts (CFU-Fs) and cell proliferation [96,97].

Interleukin-17A and Osteogenic Induction

The first investigation demonstrating that IL-17A could promote MSC osteogenic differentiation was published in 2009 [95]. Primary human MSCs treated with the cytokine showed increased proliferation and migration. Moreover, IL-17A activated TRAF6-Act1-nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX)1/reactive oxygen species (ROS)-MEK-ERK mitogen-activated protein kinase (MAPK) signaling, alongside the increased expression and activity of alkaline phosphatase (ALP) [95].

IL-17A-induced osteoblastogenesis may rely on the inflammatory phase or polarization of MSCs. Based on Toll-like receptor (TLR) expression, MSC can exhibit two polarized phenotypes: MSC1 for TLR4+ cells and MSC2 for TLR3+ cells, which have different inflammatory activities [98]. In experiments with mouse-derived MSCs, IL-17A was found to induce MSC2 polarization through Wnt10b/RUNX2 signaling and was associated with increased bone mineralization. Moreover, MSC2 cells were linked to new bone formation in a murine ankylosing spondylitis (AS) model. Mononuclear cells from the peripheral blood of AS patients with newly formed bones had notably elevated levels of *IL-17A* mRNA compared to normal individuals [99].

IL-17A is critical during the excessive inflammation and aberrant bone formation in AS, thus resulting in bony ankylosis. Elevated IL-17A basal levels in serum and synovial fluid have been observed in AS patients. In AS-derived MSC-like primary bone-derived cells, IL-17A increases ALP activity and mineralization by activating the Janus kinase 2 (JAK2)/signal transducer and activator of transcription (STAT)3-mediated expression of RUNX2 and cytosine-cytosine-adenine-adenine-thymine

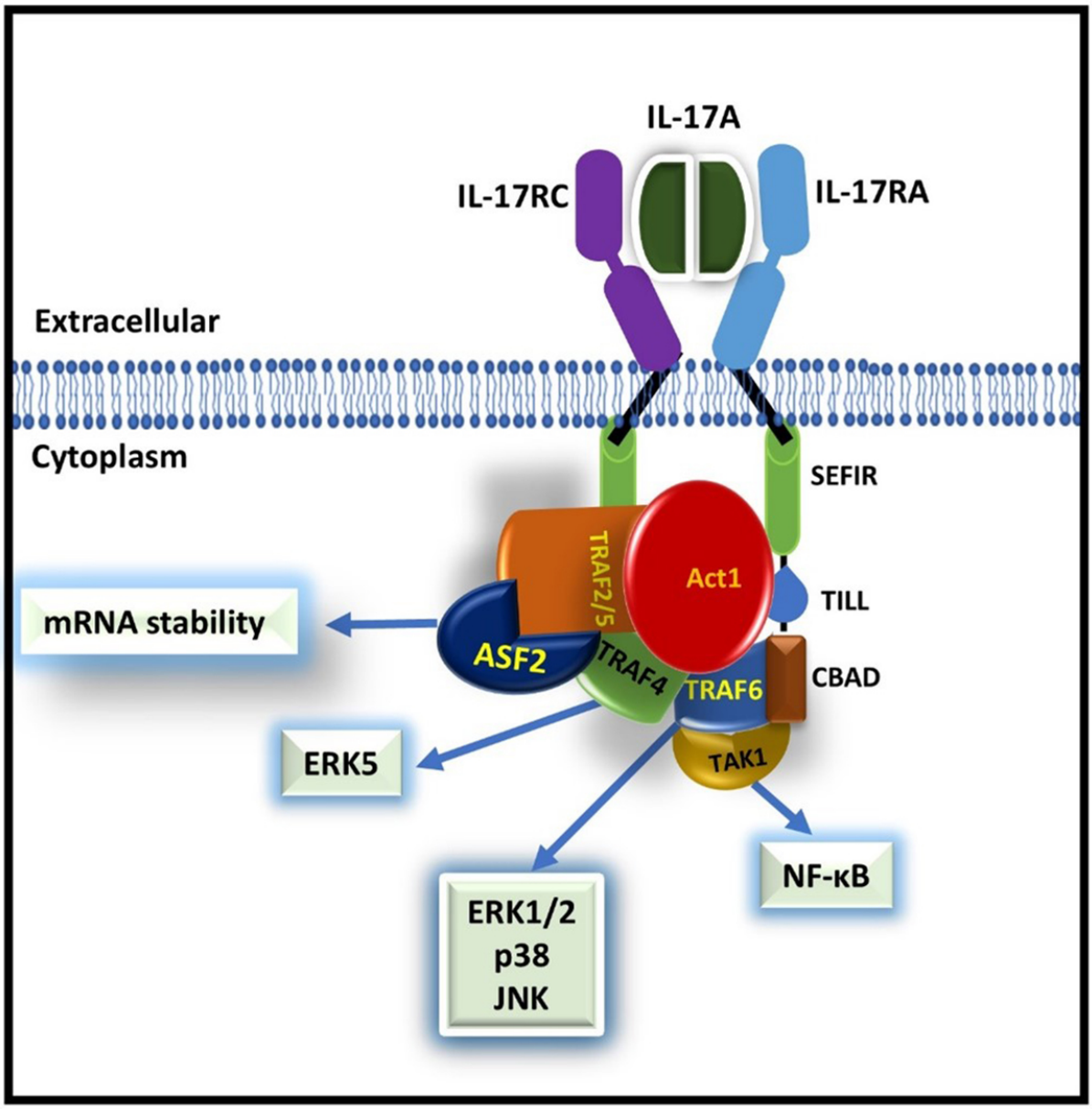

Fig. 1. Interleukin-17A signaling overview. IL-17A in a dimeric form binds to the cell surface receptor complex comprising IL-17RA and IL-17RC triggering adaptor protein Act1 intracellular interaction. Afterward, TRAF effector proteins associated with Act1: namely, the Act1-TRAF6 complex promote activation of NF-κB and mitogen-activated protein kinases ERK1,2, p38, and JNK; in turn, Act1-TRAF4 complex induces activation of ERK5, while Act1-TRAF2/5 complex regulates the mRNA stability. TRAF, tumor necrosis factor (TNF) receptor-associated factor; IL-17A, Interleukin-17A; IL-17R, IL-17 receptor; ERK1,2, extracellular signal-regulated kinase1,2; JNK, Jun N-terminal kinase; NF-κB, nuclear factor-κB; SEFIR, SEF/IL-17 receptor; Act1, NF-κB activator 1; ASF2, alternative splicing factor-2; TAK1, transforming growth factor beta-activated kinase-1; TILL, TIR-like loop; CBAD, C/EBP-β (cytosine-cytosine-adenine-adenine-thymine (CCAAT)/enhancer binding protein β) activation domain. The figure was created with PowerPoint for Microsoft 365, Microsoft, Redmond, WA, USA.

(CCAAT)/enhancer-binding protein beta (C/EBPβ) [100, 101]. In the meantime, treatment with bimekizumab to block IL-17A overcomes the capacity of the human periosteum-derived cell (hPDC)-derived serum to promote osteogenic commitment in AS patients, as demonstrated by reduced RUNX2 expression [102].

In line with this, IL-17A also contributes to chronic rhinosinusitis (CRS) neo-osteogenesis, a complex paranasal sinus mucosa disorder involving new bone formation, particularly in “difficult-to-treat” CRS patients [103,104]. CRS patients with neo-osteogenesis showed increased levels of RUNX2 and IL-17A. Additionally,

treating the murine cell line C2C12 with nasal tissue extracts reinforced the idea that IL-17A promotes RUNX2 expression to enhance new bone generation in CRS patients [105].

Furthermore, by secreting IL-17A, $\gamma\delta$T cells stimulate bone generation and accelerate fracture repair in a drill-hole-injured femur murine model. IL-17A is induced during the early phase of bone fracture repair and stimulates mesenchymal progenitor cell proliferation and osteogenesis, thus promoting bone formation. On the contrary, a bone-repair impairment in mice$^{IL-17A-/-}$ is observed due to reduced osteoblastic differentiation, while osteoclastic bone resorption remains unchanged [106].

Intriguingly, IL-17A improves osteocytes' ability to promote osteogenesis in mouse BM-derived MSCs. IL-17A triggered osteoblastogenesis by activating protein kinase B (PKB), signal transducer and activator of transcription 3 (STAT3), and the ERK1/2 pathways, increasing ALP, RUNX2, OCN and COL1 expression. In coculture conditions, IL-17 increases IL-6 and IL-1β secretion in osteocytes and MSCs, mediating the promotion of MSC osteogenic differentiation. When IL-6 or IL-1β are blocked, an inhibition of IL-17A capacity to activate PKB, STAT3, and ERK1,2 occurs on MSCs. These observations suggest that this cytokine may promote MSC osteogenesis by enhancing the interaction between MSCs and osteocytes [107].

Interestingly, IL-17A synergizes BMP-2 osteogenic activity in human MSCs both *in vitro* and *in vivo*. This cytokine significantly increases BMP-2's capacity to induce matrix mineralization [108]. At the same time, this factor suppresses osteoclast differentiation and enhances heterotopic bone generation induced by BMP-2 in bisphosphonate zoledronic acid (ZOL)-coated ceramic scaffolds in a rabbit model. Co-delivery of BMP-2 and IL-17A doubled the bone volume after 12 weeks compared to BMP-2 alone in subcutaneous ceramic scaffold implantation. IL-17A also induced connective tissue growth and recovered the capability of BMP-2 to promote angiogenesis and connective tissue generation which was prevented by ZOL [109].

Furthermore, IL-17A induces osteoblast differentiation in MSCs obtained from dental tissues by stimulating the expression of osteogenic-associated protein factors, such as RUNX2 and OCN, and matrix mineralization in dental-pulp-derived MSCs [110]. This cytokine also promotes osteogenesis in MSCs derived from stem cells Human Exfoliated Deciduous teeth (SHED), where treatment with IL-17A increased cell proliferation during the early stage while inducing ALP expression after two weeks of incubation. Additionally, IL-17A treatment downregulated the expression of stemness markers, such as c-Myc and Nanog, while upregulating RUNX2, COL1, OPN, OCN, and OPG, with a decrease in RANKL expression [111].

IL-17A has a multifaceted role in regulating bone metabolism. In this sense, in mouse calvarial bone osteoblasts, IL-17A regulates RANKL expression through the JAK2-STAT3 transduction pathway, with its effects depending on the cytokine dose. At low doses, IL-17A induces autophagy, whereas at high doses, it activates JAK2-STAT3, protecting cells from autophagy induced by rapamycin, an mammalian target of rapamycin (mTOR) inhibitor [112]. In addition, inhibiting autophagy with 3-methyladenine, a phosphoinositide 3-kinase (PI3K) inhibitor, improves the function of the IL-17A-JAK-STAT3 signaling pathway. Moreover, at high levels, IL-17A promotes ALP induction along with the mineralization of osteoblastic progenitors, increasing the levels of both *OPG* and *RANKL* mRNA transcripts and leading to a reduced OPG/RANKL ratio. Thus, high IL-17A levels modulating the OPG/RANKL ratio stimulate bone turnover by affecting the osteoblastogenesis and osteoclastogenesis balance [112].

In addition, the interaction of IL-17A and TNF-α improves osteogenesis. IL-17A and TNF-α synergistically ameliorate ALP activity and matrix mineralization, promoting the Schnurri-3 expression essential for osteoblast function [113]. Combined IL-17A and TNF-α treatment also stimulates the type II TNF receptor (TNFRII), explaining their synergism in MSC osteogenesis [114]. Similarly, in RA and OA, this combination positively influences the osteogenesis of fibroblast-like synoviocytes (FLSs) *in vitro*, although with diverse potencies [115]. Furthermore, simultaneous bone destruction and osteophyte formation in OA have been observed, related to a reduced joint destruction rate [116]. FLS cells are a mesenchymal cell type that significantly shapes the stromal microenvironment in bone diseases associated with arthritis [117]. IL-17 potentiates mineralization and Wnt5a expression in RA- and OA-derived FLSs when chemically induced *in vitro*. In *ex vivo* assays using RA bone explants, IL-17A alone or combined with TNF-α significantly decreases the bone volume over the total volume (BV/TV) ratio. In contrast, only the combination decreases this ratio in OA bone explants. Thus, IL-17A improves TNF-α-induced FLS osteogenesis in RA and OA [118].

Also, IL-17A or Th17-cell-coculture conditions promote ligamentum flavum cells (LFCs) toward osteogenic differentiation via β-catenin signaling. These results imply the contribution of IL-17A in thoracic heterotopic ossification of the ligamentum flavum and, thereby, thoracic spinal stenosis [119]. IL-17A inhibition prevents abnormal bone soft-tissue formation in traumatic heterotopic ossification. The administration of IL-17A blocking antibodies in a mouse model of traumatic heterotopic ossification attenuates ectopic bone formation alongside reduced β-catenin signaling activity [120].

In addition, when incubated with osteogenic media, IL-17A induces osteogenic differentiation in murine calvarial progenitor osteoblastic cells; increases ALP (*Alp*), OSX (*Osx*), bone sialoprotein (*Ibsp*), and OPN (*Spp1*)

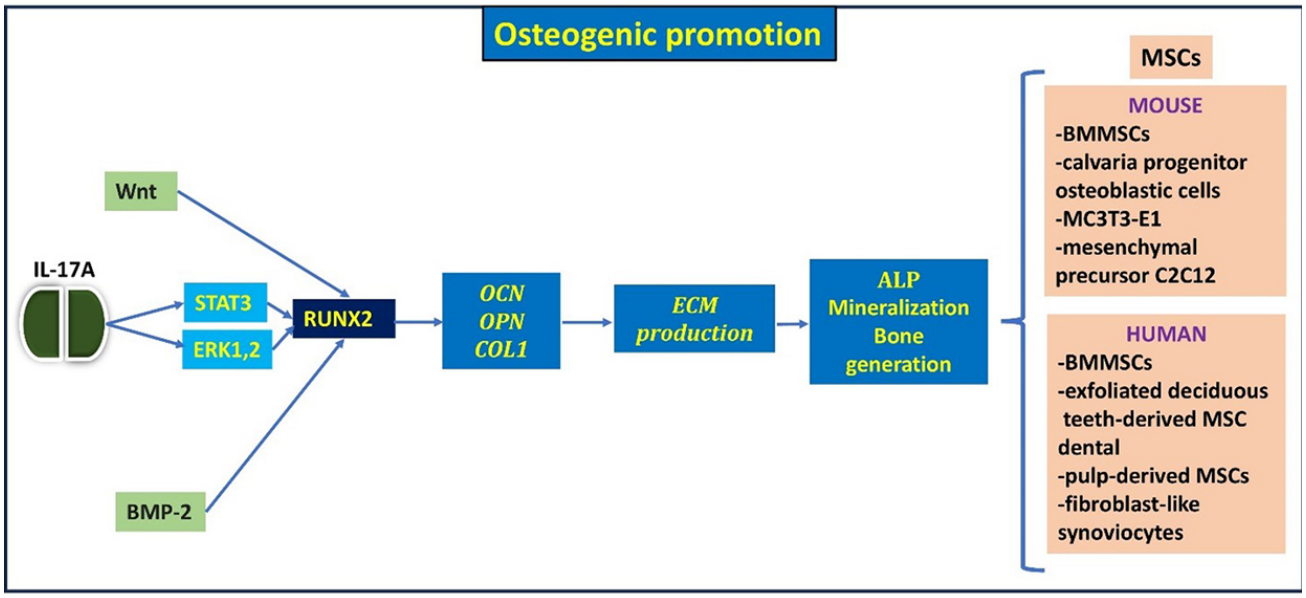

Fig. 2. IL-17A promotes MSC osteogenic differentiation. IL-17A, mainly via ERK1,2 and STAT3 signaling, can induce the osteogenic RUNX2 transcription factor expression, which in turn facilitates the expression of critical protein factors conforming to a mature extracellular matrix, such as OCN, OPN, OPG, and COL1, and terminal osteogenic differentiation. At the same time, IL-17A cooperates with BMP-2 and Wnt to potentiate the indicated MSCs' differentiation towards osteogenic lineage. Blue arrows indicate induction of expression or activation. STAT3, signal transducer and activator of transcription 3; Wnt, Wingless-related integration site; BMP-2, bone morphogenetic protein-2; RUNX2, Runt-related transcription factor 2; OCN, osteocalcin; OPN, osteopontin; COL1, collagen-type 1; OPG, osteoprotegerin; ECM, extracellular matrix; ALP, alkaline phosphatase; MSCs, mesenchymal stromal/stem cells; BMMSCs, bone marrow stromal cells. The figure was created with PowerPoint for Microsoft 365, Redmond, WA 98052, USA.

mRNA expression; and promotes mineralization. Furthermore, IL-17A promotes the recovery and regeneration of bone tissue in a mouse calvarial defect model treated with beta-tricalcium phosphate [121]. Moreover, IL-17A can stimulate the osteogenesis of mouse calvarial (MC)3T3-E1 cells, which are commonly used as a pre-osteoblast cell line to study osteoblastic processes [122]. For example, IL-17A promotes MC3T3-E1 osteoblastic differentiation under chemical osteogenic induction by activating the PI3K-Ras-related C3 botulinum toxin substrate (RAC)-β serine/threonine-protein kinase (AKT2) pathway. Meanwhile, AKT2 knockdown hinders the MC3T3-E1 cell progression to osteogenesis promoted by IL-17A, as evidenced by the impaired expression of *RUNX2*, *ALP*, and *OCN*, ALP activity, and mineralization [123]. More recently, IL-17 protects primary mouse mandibular osteoblasts from osteogenesis inhibition by the ferroptosis activator erastin. In this experimental periodontitis model, the cytokine potentially reverses osteoblast ferroptosis via STAT3 activation and the interaction of phospho-signal transducer and activator of transcription 3 (p-STAT3) with nuclear factor erythroid-2-related factor (Nrf)2 [124].

The main biological and molecular aspects of IL-17A promoting osteogenesis are summarized in Fig. 2.

IL-17A Inhibits MSC Osteogenesis

IL-17A has also been postulated to exert anti-osteogenic functions. For instance, this factor inhibits human periodontal ligament stem cell (PDLSC) proliferation, migration, and osteogenic differentiation through ERK1/2 and JNK MAPK, along with decreasing ALP activity and RUNX2, Specificity protein (SP)7, and OCN expression [125,126]. Meanwhile, doxycycline confers resistance to PDLSC to osteogenesis inhibition by IL-17A. Mechanistically, this antibiotic inhibits cytokine-induced matrix metalloproteinase 2 (MMP2), cell migration, and IL-6 expression, greatly enhancing ALP activity and expression [127].

IL-17A also inhibits calvarial cells' osteocyte differentiation *in vitro*, reducing *Alp* expression and mineralization. This inhibition is reflected in the prolonged filling and repair of calvarial defects *in vivo* [106,128]. Moreover, in an experimental mouse periodontitis model, IL-17A triggered NF-κB activation and inhibited osteoblasts' and osteocytes' osteogenic capacity *in vitro* [129]. Furthermore, the Inhibitory kappa B (IκB) kinase (IKK)-NF-κB dependent β-catenin degradation induced by IL-17A inhibits murine MSC osteogenic differentiation. In turn, the IKK-NF-κB inhibition improves the capacity of MSCs to enhance bone generation *in vivo*. Accordingly, treating BMMSCs with IL-17A demonstrates compromised os-

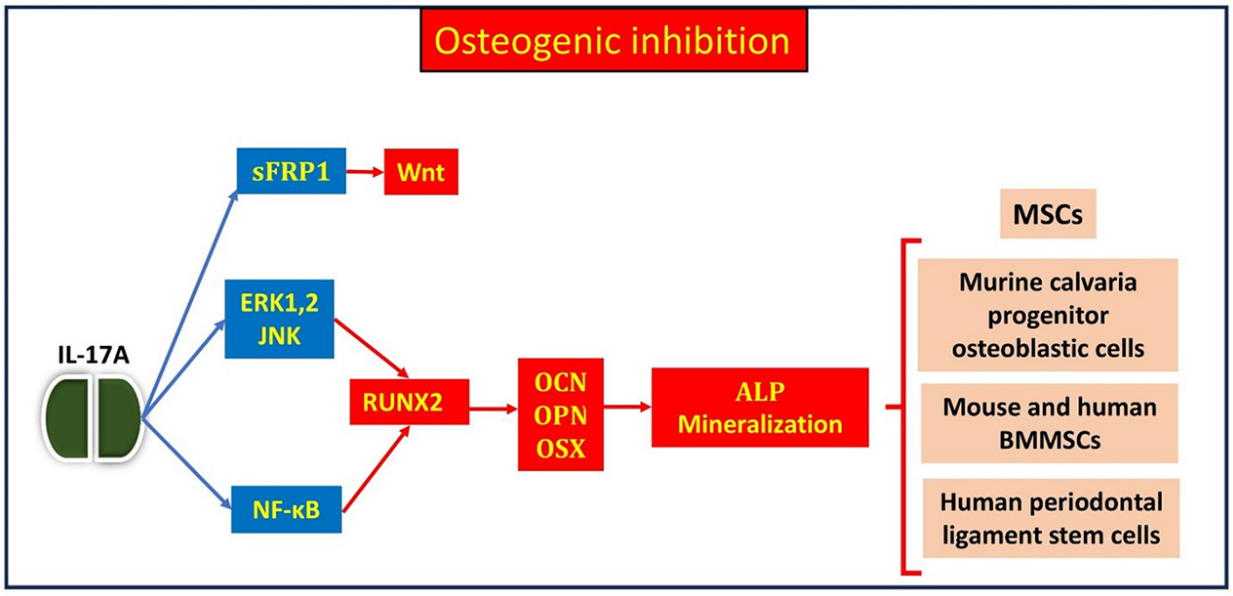

Fig. 3. IL-17 inhibits MSC osteogenic differentiation. IL-17A via activation of ERK1,2 and JNK, or NF-κB may repress RUNX2 expression, producing a lack of OCN and OPN production and osteogenic differentiation. Moreover, IL-17A may induce sFRP1, which in turn inhibits Wnt. Blue arrows indicate expression or activation induction, while red arrows indicate repression or inhibition. sFRP1, secreted frizzled-related protein-1; OSX, Osterix. The figure was created with PowerPoint for Microsoft 365, Microsoft, Redmond, WA, USA.

teogenesis paralleled by an inhibition of RUNX2, ALP, and OPN expression and calcium-phosphate mineralization [130].

In addition to osteogenesis inhibition, IL-17A has been found to provoke Wnt factor inhibition by increasing the expression of the Wnt signaling pathway inhibitor secreted frizzled-related protein (sFRP), a decoy Wnt receptor [131]. Specifically, murine calvaria-derived osteocytes treated with this cytokine cannot display the osteogenic program due to increased sFRP1 production and decreased sFRP3 expression [132,133]. IL-17A can also inhibit Wnt signaling and bone formation by upregulating sclerostin (SOST) [134,135]. Specifically, the elevated SOST expression in adipose-derived MSCs (ADSCs) promotes Th17 cells' increased frequency. Consequently, the increment of IL-17A promotes ADSCs' adipogenic differentiation to the detriment of their osteogenic capacity [136].

IL-17A also contributes to secondary osteoporosis in systemic SLE patients. The transplantation of human BMMSCs and SHED cells ameliorated and recovered bone density in autoimmune-prone MRL/Mp-Ipr/lpr (MRL/lpr) mice, a model resembling human SLE. Human BMMSC transplantation rescued compromised functions and restored bone metabolism in mice. This effect mainly relies on overcoming aberrant IL-17A expression in the BM of recipient MRL/lpr mice, supported by its systemic inhibition using blocking antibodies [137,138].

The main biological and molecular aspects of IL-17A-inhibiting osteogenesis are summarized in Fig. 3.

Perspectives of IL-17A and MSC in Bone Disease and Orthopedics

As mentioned above, IL-17, as part of the inflammation response during bone injury, plays a double role in the osteogenesis of MSCs. The promoting role of IL-17 on osteogenesis, although it can be relevant for bone repair and regeneration, has not yet been addressed at the clinical level. Nevertheless, high levels of acute inflammation seem to promote ectopic ossification. It is plausible that IL-17 positively influences ectopic bone formation, since it mediates inflammation in acute inflammatory pathologies, and it may promote traumatic heterotopic ossification in animal models, making IL-17A a clinical target for ectopic bone-formation therapies [120,139].

Since IL-17A contributes to bone damage in several inflammation-mediated bone diseases, such as RA, PsA, and SLE [140,141], much more attention has been generated in producing clinical strategies targeting IL-17. Consequently, several anti-IL-17 antibody therapies have been generated, and numerous significant clinical trials have established that therapies targeting IL-17A effectively prevent structural bone damage [11,142,143]. IL-17A neutralization may also alleviate the severity of metal-delayed type hypersensitivity (DTH) immune reactivity in total joint arthroplasty orthopedic procedures [144].

Meanwhile, MSCs have elicited great expectations for their cellular applications in bone repair and regeneration due to their capacity for self-renewal, differentiation, and

immunomodulation. MSCs may promote bone healing by secreting cytokines and growth factors that facilitate bone generation; undergo osteoblastic differentiation and initiate bone repair; secrete different biomolecules to promote osteo-regeneration; and aid in the treatment of pathological bone defects such as OA, cartilage defects, osteonecrosis, bone defects, and spinal defects [28,145,146].

Although inflammation is the crucial first step for bone healing, the duration and aggressivity of the inflammatory response may influence bone healing because acute inflammation may promote bone generation. In contrast, excess acute inflammation or chronic inflammatory conditions are related to osteogenesis inhibition [9,147].

To date, there have been no clinical trials or applications addressing the potential of IL-17 to influence MSC osteogenesis for bone repair and regeneration or bone diseases. Its divergent actions in promoting osteogenesis or inhibiting osteoblastogenesis rely to an extent on the inflammatory status of the MSCs. This status should be cautiously considered before undertaking cellular therapy for medical applications, and not only for the selected cells; the host's inflammatory status should also be considered and can be an important challenge in MSC selection for cellular therapies.

According to the inflammatory signal status of MSCs, IL-17A expressed at high levels and released after bone injury influences MSCs towards an early osteoprogenitor/osteoblast cell fate, thereby contributing to osteo-repair and -regeneration towards functional bone recovery. However, IL-17A can also function as an anti-osteogenic factor that may result in bone turnover disbalance and bone tissue loss. At the molecular level, two signaling pathways are involved in osteogenesis that oppose each other and may play a significant role in determining how IL-17A affects the osteogenic ability of MSCs. These antagonistic pathways could influence the capacity of IL-17A to either promote or inhibit the process of bone formation orchestrated by MSCs. Activation of the pro-osteogenic Wnt signaling pathway or the anti-osteogenic NF-κB pathway can modulate the cellular response to IL-17A [52,148,149]. The interplay between these signaling pathways may ultimately dictate whether IL-17 functions as a pro- or anti-osteogenic factor. Therefore, when determining NF-κB signaling and Wnt inhibitors, biomarkers such as sFRPs and SOTS may indicate the potential of IL-17A as an anti-osteogenic factor. When cells display low NF-κB activity, the Wnt signaling pathway can operate and promote MSC osteoblastogenesis. In this scenario, IL-17 can function as a pro-osteogenic factor in cooperation with this signaling pathway.

Another subject to be considered is that MSCs are immunosuppressive cells and may control tissue inflammation [150]. They can be licensed to reinforce their immunosuppressive properties that may facilitate bone repair and regeneration. Licensed or preconditioned MSCs may undergo *in vitro* treatment with proinflammatory cytokines such as IL-17A [147,151]; in this condition, licensed MSCs may also display osteogenic ability and potentially undergo enhancement by IL-17A during the acute phase of bone repair. Nevertheless, this hypothesis needs to be experimentally challenged. Another possible aspect worthy of study is that improving MSCs' immunosuppressive function by licensing IL-17A may also regulate the levels of locally secreted IL-17 during the inflammatory response in bone damage or orthopedic applications. MSCs may convert Th17 cells to low-IL-17A-producing cells [152], which may impede the cytokine's harmful actions on musculoskeletal tissues.

Combinatory applications of IL-17A and MSCs in bone healing and disease are a developing area of research. Much more investigation should be carried out to define the best conditions for targeting IL-17A with regard to the inflammatory status of MSCs and host recipients that may influence the outcome of bone therapies in clinical applications.

Conclusion

Bone development, repair, and regeneration are intricately regulated by many microenvironmental factors that influence bone homeostasis, such as ECM proteins and interactions, pro- and anti-inflammatory cytokines, and growth factors. Inflammation is crucial in controlling cell differentiation during bone repair, with inflammation preceding and being essential for bone healing. After a bone injury, IL-17A expression and secretion greatly increase, influencing MSCs towards an osteoprogenitor cell fate and thereby contributing to osteo-repair and -regeneration towards functional bone recovery. However, IL-17A also inhibits osteogenesis, provoking bone turnover disbalance and bone tissue loss. With a deeper understanding of IL-17A-related bone conditions, it will be possible to explore and identify more effective therapeutic approaches benefiting patients with musculoskeletal conditions.

Availability of Data and Materials

Not applicable.

Author Contributions

JFS: conceptualization, investigation, writing-original draft, writing-review & editing, validation, supervision. The author contributed significantly to editorial changes of important content. The author read and approved the final manuscript. The author has participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The author declares no conflict of interest.

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