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ABOUT COVER

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Regulation of the mesenchymal stem cell fate by interleukin-17: Implications in osteogenic differentiation

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Abstract

Bone regeneration is a tightly regulated process that ensures proper repair and functionality after injury. The delicate balance between bone formation and resorption is governed by cytokines and signaling molecules released during the inflammatory response. Interleukin (IL)-17A, produced in the early phase of inflammation, influences the fate of osteoprogenitors. Due to their inherent capacity to differentiate into osteoblasts, mesenchymal stem/stromal cells (MSCs) contribute to bone healing and regeneration. This review presents an overview of IL-17A signaling and the leading cellular and molecular mechanisms by which it regulates the osteogenic differentiation of MSCs. The main findings demonstrating IL-17A's influence on osteoblastogenesis are described. To this end, divergent information exists about the capacity of IL-17A to regulate MSCs' osteogenic fate, depending on the tissue context and target cell type, along with contradictory findings in the same cell types. Therefore, we summarize the data showing both the pro-osteogenic and anti-osteogenic roles of IL-17, which may help in the understanding of IL-17A function in bone repair and regeneration.

Key Words: Interleukin-17; Mesenchymal stem cells; Osteoblast; Bone; Osteogenesis; Inflammation

Core Tip: The immune system closely interacts with the bone system in health and disease. Inflammation plays a strategic role in bone homeostasis and turnover. A pro-inflammatory cytokine interleukin-17 (IL-17) is produced in high amounts after bone damage and can influence mesenchymal stem cells' fate toward early osteoprogenitor cells, either as a pro-osteogenic or an anti-osteogenic factor. Although these divergent IL-17 roles in bone formation are still not well understood, different conditions of the local microenvironment, the extent of inflammation, and the specific nature and stage of osteoprogenitor cells can influence the response to this cytokine, affecting the final cell differentiation outcome.

INTRODUCTION

The interleukin-17 (IL-17) cytokine was first described in 1993 as a cytotoxic T lymphocyte antigen 8 (CTLA8) and was, subsequently, in 1995, reported to share 57% of its sequence homology with the herpes virus saimiri gene 13 (HVS13). Both HVS13 and CTLA8 were shown to costimulate T-cell proliferation by binding to a novel cytokine receptor and were named IL-17, vIL-17, and IL-17R, respectively[1,2]. Later on, Park *et al*[3] defined the cellular requirements for the differentiation of naïve CD4 T-cells into effector T helper cells with the capacity to express and secrete IL-17. This resulted in the discovery of a new subset of T helper cells with proinflammatory functions, referred to as T_H17 cells[4]. Today, IL-17 is recognized as a founding member of the IL-17 family that comprises the cytokines IL-17A (initially named IL-17) through IL-17F, which were discovered *via* screening for homologous genes[5]. By producing IL-17A and IL-17F, T_H17 cells participate in host protection against external pathogens and recruit macrophages and neutrophils to the infection site[6,7].

The dysfunctional regulation of T_H17 may exacerbate the pathogenesis of multiple inflammatory and autoimmune disorders, such as sepsis, pneumonia, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), allograft rejection, and cancer[4,8]. Specifically, the six IL-17 cytokines are secreted glycosylated proteins with molecular weights of about 20-30 kDa and share 20%-50% of their sequence homology with IL-17A. IL-17 family members exhibit a conserved protein C-terminus with two intramolecular disulfide bridges formed by four cysteine residues. Moreover, IL-17s belong to the cystine knot fold superfamily since they dimerize similarly to the nerve growth factor subfamily[8-13]. Furthermore, IL-17A and IL-17F form either homodimers or heterodimers and are co-expressed by linked genes on chromosome 6[6,14,15]. It is well known now that, beyond T_H17 cells, many cell types can produce IL-17, including almost all innate and adaptive immune cells[4,6].

IL-17 cytokines exert their actions by binding to the IL-17 receptor (IL-17R) family, composed of five receptor types (IL-17RA to IL-17RE)[5]. Although its expression level varies widely, IL-17R is expressed ubiquitously and is mainly characterized by a shared SEF/IL-17R (SEFIR) motif in the intracellular domain and two fibronectin III-like regions (FN1 and FN2) within the extracellular environment[5,16,17]. In addition, all IL-17 isoforms bind to IL-17RA, which forms heterocomplexes with other IL-17R subtypes responsible for ligand-binding specificity[8,18].

IL-17A initiates signaling by binding to an IL-17RA/IL-17RC receptor complex. This binding triggers the multifunctional adaptor Act1, a U-box E3 ubiquitin ligase interaction with IL-17R *via* the SEFIR domain (Figure 1). Next, the IL-17 downstream intracellular signaling is activated *via* homotypic interactions between the tumor necrosis factor (TNF) receptor-associated factor (TRAF)6/transforming growth factor β (TGF-β)-activated kinase 1 (TAK1) complex with Act1. This signaling includes nuclear factor-κB (NF-κB) and mitogen-activated protein kinases (MAPK) (ERK1,2, p38, and JNK). Similarly, the activated IL-17/IL-17R/Act1 complex can signal *via* the
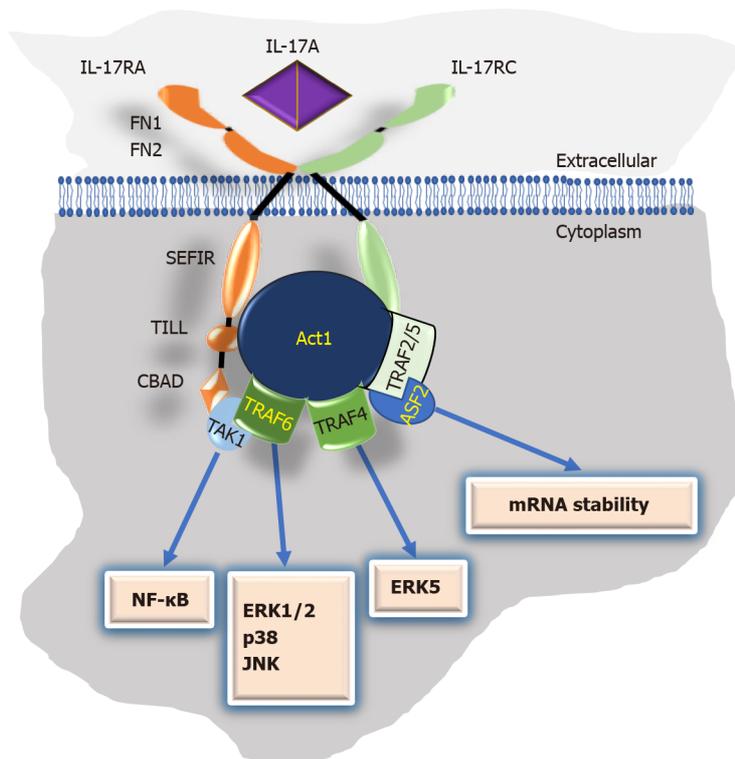
Figure 1 Overview of interleukin-17A signaling. Interleukin (IL)-17A in a dimeric form binds to the cell surface receptor complex comprising IL-17RA and IL-17RC, which triggers the intracellular interaction with the adaptor protein Act1. Then, tumor necrosis factor receptor-associated factor (TRAF) effector proteins associated with Act1: Act1-TRAF6 complex promotes activation of nuclear factor-kB and mitogen-activated protein kinases ERK1,2, p38, and JNK; Act1-TRAF4 complex induces activation of ERK5; and, Act1-TRAF2/5 complex modulates mRNA stability. For more details, see the text. IL-17: Interleukin-17; TRAF: Tumor necrosis factor receptor-associated factor; NF-κB: Nuclear factor-κB.

TRAF4/MEKK3/MEK5/ERK5 axis. Finally, the noncanonical signaling of IL-17A involves a TRAF2/5-human antigen R (HuR)-alternative splicing factor (ASF or SF2) cascade that results in the control of mRNA stability of IL-17-targeted inflammatory cytokine and chemokine genes[5,18-20].

Mesenchymal stem/stromal cells (MSCs) are multipotent stromal cells that were first described in the bone marrow (BM) regarding their capacity to support hematopoiesis after heterotopic transplantation in a nude mouse model[21,22]. MSCs display a spindle fibroblast-like shape and are capable of self-renewal. Moreover, when stimulated, both *in vivo* and *in vitro*, they can differentiate into several mesodermal cell types[23,24]. Moreover, it is now well known that MSCs can also differentiate into nonmesodermal lineages, such as hepatocytes, neurons, and pancreatic cells, among others[24].

MSCs are defined by standardized criteria for their identification and characterization. In 2006, the International Society for Cellular Therapy proposed a set of minimum standards to characterize MSCs: fibroblast-like morphology, plastic adherence, three mesodermal lineage differentiation capacities (adipocytes, osteocytes, and chondrocytes), and specific immunophenotype surface markers[25], whereby more than 95% of MSCs should express CD73, CD90, and CD105. Meanwhile, to avoid hematopoietic cell contamination, leukocyte markers CD45, CD34, CD14 or CD11b, CD19 or CD79α, and HLA-DR should be expressed in less than 2% of the cell population. Recently, additional cell surface markers have been identified that ensure the isolation of clonogenic MSCs such as STRO-1, CD29, CD44, CD106, CD146, and CD27 and epidermal growth factor receptor, insulin-like growth factor (IGF) receptor, and nerve growth factor receptor[26].

MSCs are present in almost all adult tissues[27]. Adipose tissue, BM, and dental tissue are the preferred sources for preclinical and clinical research[24,28,29]. Furthermore, the usage of adult MSCs is not compromised by the biological and ethical concerns that surround their embryonic counterparts. Thus, they can be used as autologous transplants, which has opened up new opportunities for tissue regeneration and bioengineering, as well as for cell-based clinical applications[30-32]. Moreover, when transplanted, MSCs do not manifest tumorigenicity, which is an advantage compared to induced pluripotent stem cells[33,34].

Under homeostatic conditions, MSCs are hypoimmunogenic and capable of evading immune system recognition. In addition, they express low class I major histocompatibility complex (MHC) molecules and lack class II MHC and costimulatory molecule (CD40, CD80, and CD86) expression. These characteristics make MSCs suitable for allogeneic transplantation[35,36]. Likewise, MSCs possess remarkable immunosuppressive, immunomodulatory, and anti-inflammatory functions, accompanied by antimicrobial properties. Thus, MSCs are meaningful candidates to be studied and potentially may be used in therapies for fracture healing and bone regeneration[37-40].

THE BONE STRUCTURE AND FUNCTION

Bone is a supportive tissue contributing to locomotion, soft tissue and vital organ protection, blood pH regulation, and calcium and phosphate homeostasis. It also provides a functional milieu for blood production in the BM and progenitor cell niche formation. In this regard, the bone contains both mesenchymal and hematopoietic cell compartments[41-43].

Bone tissue is mainly composed of two interrelated compartments: (1) Like connective tissue, bone is rich in the extracellular matrix (ECM) and abundant in organic collagen fibers (comprising about 90% of the matrix proteins) and inorganic hydroxyapatite (a naturally occurring mineral significant for bone reinforcement)[43-46]; and (2) The cellular components of bone mainly encompass osteoprogenitors, osteoblasts, osteocytes, and osteoclasts[45,47,48].

Osteoblasts are differentiated cells originating from BM MSCs. Undifferentiated MSCs reside in the periosteum, which covers the bone surface. The osteogenic process occurs in sequential events, including MSC recruitment to bone remodeling areas, followed by cell proliferation and subsequent lineage commitment[49]. In the beginning, MSCs are committed to generating actively proliferating pre-osteoblasts, which at this early stage do not produce ECM proteins. Next, cells cease proliferation and start to secrete type I collagen, proteoglycans, and other noncollagenous proteins. Afterward, the mineralization process occurs with the phosphates released by osteoblast-associated phosphatases, which combine with calcium to form hydroxyapatite crystals. Once a functional ECM is generated, osteoblasts differentiate into osteocytes, long-lived cells with an average half-life of 25 years, embedded within lacunae[49].

Interestingly, osteocytes encompass approximately 90%-95% of bone cells and are recognized as the principal regulators of bone homeostasis since they contribute to bone formation and resorption during bone remodeling. In addition, osteocytes may act as sensors for organic and inorganic molecules during mechanical stimuli to remodel the environment, thus contributing to the proper maintenance of bone tissue functionality[50-55]. On the other hand, osteoclasts are large multinucleated bone-resorbing cells that originate from the fusion of myeloid precursors of the monocyte/macrophage lineage and participate in bone degradation, bone turnover, and remodeling[56,57].

Bone tissue is created by intramembranous ossification or endochondral ossification. In the first place, direct ossification occurs in the neuro and viscerocranium, flat bones, and in part of the clavicle. It is characterized by MSC-derived osteoblast condensation, which causes mature osteoblasts to evolve into osteocytes. Meanwhile, indirect endochondral ossification occurs in long bones, vertebrae, the skull base, and the posterior skull[58]. This process involves MSCs, which initiate the first round of cartilage differentiation and are later replaced by bone tissue, considerably increasing the ability to withstand mechanical compression[59].

Healthy bone is a dynamic organ with a constant balance of fine-tuned bone resorption and new tissue generation. It confers bone's ability to repair itself by continuous skeletal adjustment to mechanical forces in varying environmental conditions[41,43]. Therefore, impairment in cell differentiation can result in different bone pathologies. For example, an imbalance in BM MSC differentiation toward the adipocyte lineage, to the detriment of osteoblast/osteocyte generation, may result in bone mass loss and bone diseases such as osteoporosis[60,61].

Mechanistically, early osteogenesis stages include the expression of hedgehog proteins, Wnt/β-catenin signaling, bone morphogenetic proteins (BMPs), endocrine hormones, epigenetic regulators, cytokines, and growth factors. These events implicate complex processes of finely regulated and timely orchestrated activation of specific transcription factors to express genes that accurately define the osteoblast phenotype [60,62].

Runt-related transcription factor 2/core-binding factor subunit alpha-1 (Runx2/Cbfa1) and downstream osterix (OSX) are crucial for osteoblast differentiation. The absence of either Runx2 or OSX results in the impairment of skeleton mineralization. Moreover, Runx2 is essential for MSC commitment toward the osteogenic lineage[63]. Therefore, Runx2 is expressed early during osteogenesis. However, as the differentiation process advances, Runx2 expression is downregulated, accompanied by upregulation of OSX and β-catenin with further osteoblast maturation[60,62].

Namely, Runx2 contains a runt DNA-binding domain harbored by several enhancers and promoters, including those for the genes encoding alkaline phosphatase (ALP), collagen type 1 (COL1), osteocalcin (OC), and osteopontin (OPN). These proteins contribute to bone matrix generation and osteoblast maturation. These genes are also useful as markers for different osteogenesis stages[64-66]. The time course of events indicates that ALP is an early marker of osteogenic differentiation and mineralization in committed osteoprogenitors. In contrast, more advanced osteogenesis stages implicate COL1, osteoprotegerin (OPG), and osteonectin expression, while OC and OPN are confined mainly to the terminal differentiation phase[62,67-69]. OPG, first characterized and named for its protective role in bone remodeling[70,71], functions as a soluble decoy receptor for the cytokine receptor activator of NF-κB-ligand (RANKL) since it prevents the binding of RANKL to the receptor activator of NF-κB (RANK). Therefore, OPG inhibits osteoclastogenesis and protects bone from excessive osteoclast-mediated resorption[72].

In turn, osteonectin is a binding-calcium glycoprotein implicated in mineralization initiation, promoting mineral crystal formation[73]. Furthermore, OC is vital for bone formation and resorption inhibition[74]. Finally, OPN is an integrin-binding glycoprotein expressed at high levels by osteoblasts at the endosteal surface and regulates bone development and bone mass maintenance[75].

Several signaling factors are involved in the activation of Runx2, including wingless-type (Wnt)/β-catenin, BMPs, TGF-β1, hedgehog, and (Nel)-like protein type 1 (NELL-1)[76,77]. The Wnt/β-catenin signaling pathway may regulate osteoblastogenesis by modulation of MSC commitment to the osteoblastic lineage. The activated Wnt/β-catenin canonical pathway contributes to the induction of osteogenic regulators Runx2, distal-less homeobox 5, and OSX, which notably induces MSCs' progression into mature osteoblasts[43,78-80]. Furthermore, Wnt/β-catenin controls bone resorption by increasing the OPG/RANKL ratio[81,82]. Wnt5a induces noncanonical Wnt signaling pathways, such as the co-repressor complex, through calcium-calmodulin-dependent protein kinase II-TAK1-Nemo-like kinase signaling, to regulate MSC differentiation to osteoblasts by Runx2 induction and inhibition of the adipogenic transcription factor PPARγ expression[83,84].

In addition, a large body of experimental evidence unequivocally demonstrates that BMP signaling causes multipotent mesenchymal cells to differentiate into the osteochondral lineage and regulates the maintenance of postnatal bone and cartilage. The abundance of different types of BMPs varies in response to skeletal requirements. BMP-2, -4, -6, -7, and -9 are of particular importance in bone formation, as they activate BMP-associated Smads (Smad-1, -5, and -8) to induce Runx2 and OSX activation axes, while BMP-3 and BMP-13 present exceptions in the subfamily and act as inhibitors of osteogenic differentiation[85,86]. Moreover, inhibitor of differentiation (ID) proteins, especially ID1 and ID3, are critical effectors of BMP-induced osteoblastogenesis[87].

Furthermore, early-response genes that activate downstream BMP signaling in primary BM-MSCs include Dlx2 and 5. *In vitro* studies demonstrated that Dlx proteins mediate the expression of several osteoblast lineage genes, including Runx2, OSX[88], and osteoactivin, a positive regulator of bone formation, both *in vitro* and *in vivo*[89].

On the other hand, during osteoblastogenesis, inhibitory Smad6 can intracellularly inhibit BMP receptors. Furthermore, BMP-Smad1–Runx2 regulates Smad6 expression, while Smad6 regulates BMP and Runx2 activity in a negative feedback loop[86,90]. Likewise, Noggin, chordin, gremlin, and follistatin, which sequester BMPs and prevent binding to cell surface receptors, regulate BMP function during bone generation[86,88].

Also, systemic hormones, such as parathyroid hormone, glucocorticoids, estrogens, and local growth factors, such as bone TGF-β1/2, IGF, fibroblast growth factor 2 (FGF-2), vascular endothelial growth factor, prostaglandins, and MAPK signaling molecules, regulate MSC osteogenic differentiation[41]. Furthermore, MSC osteoblastogenesis can also be induced *in vitro* by adding a combination of dexamethasone, beta-glycerophosphate, and ascorbic acid to the cell culture medium[91].

IL-17A AND MSCS: THE OSTEOGENIC LINK

Bone homeostasis is a finely regulated process relying on the interplay between the immune and musculoskeletal systems[92]. Indeed, the skeletal and immune systems share several regulatory biomolecules, including growth factors, proinflammatory and inflammatory cytokines, and other signaling molecules[93]. Inflammation plays a strategic role in bone homeostasis and turnover in several inflammation-associated diseases and events, such as bone fracture healing, periodontitis, erosive arthritis, osteoarthritis (OA), chronic rhinosinusitis (CRS), and spondyloarthropathy[92,94].

Several immune cell types (*e.g.*, macrophages, neutrophils, and T cells) infiltrate injured bone tissue and regulate new bone formation during normal and dysfunctional bone repair and regeneration. In this sense, cytokines such as IL-6, TNF-α, and IL-17A positively contribute to the healing process. However, the same cytokines can enhance inflammation, triggering dysfunctional bone tissue regeneration and bone-associated inflammatory diseases[92]. Thereby, the immune system interacts closely with the bone system in health and disease.

By regulating bone regeneration and homeostasis, IL-17 also acts on MSCs' differentiation ability. MSCs express high levels of IL-17RA as well as the other four members of the IL-17R family[95,96], and IL-17A can induce MSC proliferation, migration, and differentiation[97]. For example, in mouse BM-MSCs, IL-17 increases CFU-F (colony-forming unit fibroblasts) average frequency and colony size and cell proliferation, mediated by p38 and ERK1,2 MAPKs[98,99]. Moreover, IL-17A induces the motility and transendothelial migration of peripheral blood MSCs *in vitro*, suggesting a possible role for IL-17 in the mobilization and recruitment of MSCs to injured tissues [95,100]. Consistently, IL-17A also induces the gene expression of matrix metalloproteases-1 and -13 in MSCs, which potentiates their capacity to degrade collagen and invade the ECM[101].

Moreover, IL-17 promotes the immunosuppressive function of mouse BM-MSCs by inducing nitric oxide (NO) and programmed death-ligand-1[102]. In addition, it enhances human BM-MSC-induced inhibition of T cells, and IL-17A-treated MSCs promote regulatory T cells expansion and function, further increasing their immunosuppressive effect[103,104].

THE PRO-OSTEOGENIC ROLE OF IL-17

One of the first pieces of evidence that IL-17 may regulate MSC osteogenic differentiation was provided by Huang *et al*[97]. Primary human MSCs under IL-17 treatment responded with increased proliferation and migration alongside activation of the TRAF6-ACT1-NADPH oxidase (NOX)1/reactive oxygen species-MEK-ERK MAPK pathway axis. Furthermore, IL-17 treatment induced ALP expression and activity with subsequent mineralization in cell culture. Moreover, IL-17 induced osteoclastogenesis of mononuclear cells in coculture conditions with primary human MSCs by induction of macrophage colony-stimulating factor and RANKL in primary human MSCs. Thus, IL-17 contributes to bone turnover by modulating osteogenesis and osteoclastogenesis [97].

The effect of IL-17 on MSCs' osteoblastogenesis can depend on their inflammatory stage or polarization. MSCs display two polarized phenotypes based on the expression of the surface marker Toll-like receptor (TLR): TLR4+ MSCs (also called MSC1) and TLR3+ MSCs (also called MSC2), with different inflammatory functions[105]. *In vitro*, IL-17 induces MSC2 polarization in mouse-derived MSCs through the WNT10b/Runx2 axis, concomitant with increased mineralization rates. Furthermore, in a mouse model of ankylosing spondylitis (AS), MSC2 polarization was related to new bone formation, and the PBMCs of AS patients with new bone formation expressed significantly higher IL-17A mRNA levels than those of healthy donors[106].

Interestingly, osteocytes may enhance the capacity of IL-17 to induce osteogenic differentiation of murine BM-MSCs. IL-17 triggers osteoblastic differentiation *via* the activation of AKT, STAT3, and ERK1,2 along with ALP, Runx2, OCN, and COL-1 expression. The coculture of osteocytes with MSCs under IL-17 treatment leads to an increase in IL-6 and IL-1β secretion by both cell types, which mediates the enhanced osteogenic differentiation of MSCs. Blocking either IL-6 or IL-1β inhibits IL-17-mediated activation of AKT, STAT3, and ERK1/2 in MSC. Therefore, IL-17 may potentiate MSC osteoblastic differentiation within the bone niche by increasing MSC-osteocyte interaction, further contributing to osteoblastogenesis[107].

IL-17A has recently emerged as a mediator of extensive inflammation and abnormal bone formation in AS, leading to bony ankylosis. Basal levels of IL-17A in bodily fluids (patient serum and synovial fluid) are elevated in patients with AS. Moreover, IL-17 enhanced ALP activity and mineralization in AS-derived MSC-like primary bone-derived cells by activating JAK2/STAT3-mediated both Runx2 and C/EBPβ expression[108,109]. Furthermore, in a biomimetic human periosteum-derived cell (hPDC) model, IL-17 induced osteoblastic differentiation. At the same time, blockage of IL-17 with the humanized monoclonal antibody bimekizumab suppressed serum-induced hPDC osteocommitment in AS patients, as evidenced by Runx2 expression inhibition [110].

IL-17 also plays a role in CRS neo-osteogenesis, a heterogeneous and multifactorial disorder of the paranasal sinus mucosa, which involves bone neo-osteogenesis, especially in recalcitrant CRS patients[111]. Levels of Runx2 and IL-17 were increased in tissue sections from CRS patients with neo-osteogenesis. Furthermore, IL-17A-neutralizing antibodies supported the notion that IL-17 mediates Runx2 expression in mouse mesenchymal precursor C2C12 cells treated with nasal tissue extracts. Thus, these data indicate that Runx2, induced by IL-17A, contributes to new bone formation in CRS patients through its effect on osteoblasts' activity[112].

Furthermore, Ono *et al*[113] showed that γδT cells promote bone formation by producing IL-17A and facilitate bone fracture healing in a drill-hole injured femur mouse model. Here, IL-17A was induced in the early phase of bone fracture healing and seems to accelerate bone formation by stimulating the proliferation and osteoblastic differentiation of mesenchymal progenitor cells. Conversely, bone repair impairment in *Il17a*^{-/-} mice occurs due to decreased osteoblastic-dependent bone formation, while osteoclastic bone resorption is not affected[113]. Furthermore, IL-17 enhances *in vitro* BMP-2-induced osteoblastogenesis in injury-associated MSCs.

Similarly, IL-17 synergizes with BMP-2 to induce osteoclastogenesis in human MSCs *in vitro* and *in vivo*. IL-17 dramatically increased matrix mineralization mediated by BMP-2 in human MSCs[114]. In a rabbit model, IL-17 enhanced BMP-2-induced ectopic bone formation in ceramic scaffolds coated with bisphosphonate zoledronic acid (ZOL) by suppression of osteoclasts. Doubled bone volume was observed after 12 wk of BMP-2 and IL-17 co-delivery compared to only BMP-2 in subcutaneous ceramic scaffold implantation. IL-17 induces connective tissue ingrowth and restores BMP-2-induced vascularization and connective tissue formation inhibited by the ZOL coating [115].

Dental-derived MSCs, which represent an ideal source for tissue engineering, and regenerative and dental medicine[116], also differentiate toward osteoblasts under IL-17A stimuli. For instance, IL-17 induces the osteogenic-associated proteins Runx2, OC, and ALP and mineralization in MSCs derived from dental pulp[117]. Similarly, IL-17A induces *in vitro* osteogenic differentiation in MSCs from human exfoliated deciduous teeth (SHED). IL-17 increases cell proliferation in five days of treatment while inducing ALP expression on day 14 of cultivation. Moreover, stem cell marker c-Myc and Nanog expression were downregulated after IL-17 treatment. This stem cell marker inhibition occurred concomitantly with the upregulation of osteogenesis-associated proteins—such as Runx2, COL1, OPN, OCN, and OPG—along with RANKL downregulation, which increased the OPG/RANKL ratio[118].

IL-17 may regulate RANKL expression in murine primary osteoblasts from the calvaria bone *via* JAK2-STAT3 signaling, which depends on cell autophagy in an IL-17 dose-dependent fashion. Low doses of IL-17 induced autophagy, while high doses activated JAK2-STAT 3 signaling, which could be reversed by autophagy induction with the mTOR inhibitor rapamycin[119]. Conversely, autophagy inhibition by the phosphoinositide-3 kinase (PI3K) inhibitor 3-methyladenine greatly enhanced IL-17-induced JAK2-STAT3 signaling. Furthermore, high IL-17 levels promoted ALP induction and mineralization of osteoblast progenitor cells. This treatment also increased the opg and rankl mRNA transcripts levels, and OPG and RANKL proteins were found along with a decreased OPG/RANKL expression ratio. Thus, IL-17A, depending on the dose, may regulate bone turnover, *i.e.*, osteoblastogenesis/osteoclastogenesis balance, by modulating the OPG/RANKL ratio[119].

Furthermore, IL-17A can interact with and potentiate the osteoblastic function of other inflammatory factors such as TNF-α. When used in combination, IL-17A and TNF-α further enhance ALP activity and matrix mineralization. Moreover, this combination synergistically induced the expression of Schnurri-3, a finger protein that plays a critical regulatory role in skeletal remodeling[120] and inhibits RANKL expression associated with osteogenic induction. Furthermore, IL-17A and TNF-α combination increased the type II TNF receptor (TNFRII), which may explain the synergistic effects on the osteoblastic differentiation of MSCs[121]. Similar effects of

combined IL-17A and TNF-α are observed on fibroblast-like synoviocytes (FLS) isolated from RA and OA patients, albeit with different potency[122].

Meanwhile, in OA, simultaneous bone destruction and osteophyte formation were observed and related to a reduced joint destruction rate[123]. Namely, FLS are cells of mesenchymal origin and are the dominant nonimmune cells in synovial tissues, vital elements in defining the stromal environment within arthritic bone diseases[124]. Both RA- and OA-derived FLS can perform bone mineralization *in vitro* and express Wnt5a under chemical induction, and IL-17A addition further potentiates differentiation. In addition, RA bone explants in *ex vivo* assays showed that IL-17A alone or in combination with TNF-α generates a significant decrease in bone volume over the total volume (BV/TV) ratio, while in OA bone explants, only the combination decreased BV/TV ratio. Besides those specific differences, IL-17A enhances TNF-α-induced osteoblastogenesis in both RA and OA-derived FLS[125].

Interestingly, IL-17A switches the differentiation fate of murine mesenchymal progenitor C2C12 cells. IL-17A strongly promotes osteogenic differentiation in cells cultivated in a myogenic medium mediated by ERK1,2 pathway activation and Runx2 transcriptional activity[112,126]. Moreover, IL-17A strongly inhibits myogenic transcription factor expression and reduces cell migration and urokinase-type plasminogen activator expression[127].

Moreover, IL-17A positively exerts osteogenic induction on murine calvaria progenitor osteoblastic cells under incubation with osteogenic media, since IL-17A further stimulates mineralization, along with mRNA expression of ALP (Alp), OSX (Sp7), bone sialoprotein (Ibsp), and OPN (Spp1). Furthermore, IL-17A significantly enhances healing and bone tissue formation in a mouse calvaria defect model under beta-tricalcium phosphate treatment[128]. Furthermore, IL-17A effectively induces osteogenesis in the spontaneously immortalized murine calvaria pre-osteoblast cell line MC3T3-E1, a widely used model for studying osteoblast biology[129]. For instance, IL-17A, under chemical osteogenic induction, potentiates MC3T3-E1 differentiation towards osteoblastic lineage by activation of PI3K-RAC-β serine/threonine-protein kinase (AKT2). In turn, AKT2 knockdown makes MC3T3 E1 unresponsive to osteogenic induction by IL-17A since Runx2, ALP, OCN, and relative ALP activity and mineralization are almost entirely impaired in these cells[130].

Furthermore, IL-17A synergizes with IL-6 to induce ALP activity on osteogenic differentiation of MC3T3-E1 seeded on hydroxyapatite while increasing the expression of OPG and reducing the expression of RANKL, thus increasing the OPG/RANKL ratio and suggesting the potential to reduce osteoclastogenic response[131]. The main aspects of IL-17A-induced osteogenesis are summarized in Table 1.

Other IL-17 family members also have the potential to regulate MC3T3-E1 osteoblastogenesis. Indeed, IL-17F induced osteogenic differentiation by enhancing ERK1,2/C/EBP-β/Runx2 activity[132]. This observation was confirmed by Croes *et al* [114] in an *in vitro* study where human MSCs increased ALP activity in a dose-dependent response to IL-17.

In addition to osteoblastogenesis promotion, IL-17A conversely affects adipogenesis and chondrogenesis in MSCs. Indeed, IL-17A inhibits the adipogenic differentiation of human MSCs and enhances lipolysis of differentiated adipocytes *via* upregulation of cyclooxygenase-2 expression and a subsequent increase of anti-adipogenic prostaglandin E_2[133]. Noh[134] discovered that IL-17 inhibits human BM-MSC adipogenesis and promotes osteogenesis by upregulating the leptin-JAK/STAT pathway. Also, IL-17A may inhibit adipogenic differentiation of 3T3-L1 cells, a model for adipocyte differentiation, by suppressing pro-adipogenic PPARγ, C/EBPα, and transcription factor Krüppel-like factors (KLF)-15 expression, while enhancing anti-adipogenic KLF2 and KLF3 expression[135].

Moreover, IL-17A inhibits TGF-β3-induced chondrogenic differentiation of human MSCs, mediated by impaired protein kinase A activity with a consequent reduction in SRY-type HMG box9 (SOX9) phosphorylation transcriptional activity. As a consequence, chondrogenesis-associated type II collagen (*COL2A1*), aggrecan (*ACAN*), type X collagen (*COL10A1*), and *ALP* are dose-dependently suppressed by IL-17A[136].

THE ANTI-OSTEOGENIC ROLE OF IL-17A

In contrast to the aforementioned pro-osteogenic function of IL-17A, several studies indicated an anti-osteogenic function of IL-17A (Table 2). IL-17A inhibits proliferation and migration and the osteogenic differentiation of healthy periodontal ligament stem cells through ERK1,2 and JNK MAPK[137]. Similarly, IL-17 suppresses human

Table 1 Interleukin-17 promotes osteogenesis: Summary of the main literature data		
Cells	**Differentiation effects, differentiation markers, signaling, and transcription factors**	**Ref.**
Primary human BM-MSCs	ALP, mineralization; TRAF6-ACT1-(NOX)1/ROS-MEK-ERK MAPK	Huang et al[97]
Mouse-derived BM-MSCs	Mineralization; WNT10b/RUNX2	He et al[106]
Mouse-derived BM-MSCs	ALP, RUNX2, OCN, and COL-1; AKT, STAT3, and ERK1/2	Liao et al[107]
Human MSC-like primary bone-derived cells	ALP, mineralization; JAK2/STAT3, RUNX2, and C/EBPβ	Jo et al[109]
Human biomimetic human periosteum-derived cell	RUNX2	Shah et al[110]
Mouse mesenchymal precursor C2C12	ERK1/2; RUNX2	Khalmuratova et al[112], and Kocić et al[126]
Human BM-MSCs	BMP2 synergy, mineralization	Croes et al[114]
Human dental pulp-derived MSCs	ALP and mineralization; RUNX2 and osteocalcin	Yu et al[117]
Human exfoliated deciduous teeth-derived MSC	ALP; RUNX2, COL1, OPN, OCN, and OPG	Sebastian et al[118]
Primary mouse progenitor osteoblastic cells	OPG and RANKL	Wang et al[119]
Human BM-MSC	Enhances TNF-α-induced osteogenesis; ALP and mineralization; Schnurri-3	Osta et al[121]
Human fibroblast-like synoviocytes from AR and OA	Enhances TNF-α-induced osteogenesis; RUNX2 and BMP2	Osta et al[125]
Murine calvaria progenitor osteoblastic cells	Mineralization; ALP, OSX, bone sialoprotein, and OPN	Kim et al[128]
Murine calvaria pre-osteoblast cell line MC3T3-E1	ALP and mineralization; RUNX2 and OCN; PI3K/AKT2	Tan et al[130]
Murine calvaria pre-osteoblast cell line MC3T3-E1; Seeded on hydroxyapatite	Synergizes IL-6, ALP; OPG	Sritharan et al[131]

BM: Bone marrow; MSC: Mesenchymal stem/stromal cell; ROS: Reactive oxygen species; OA: Osteoarthritis; TNF-α: tumor necrosis factor α; IL: Interleukin; ALP: Alkaline phosphatase.

Table 2 Interleukin-17 inhibits osteogenesis: Summary of the main literature data		
Cells	**Differentiation effects, differentiation markers, signaling, and transcription factors**	**Ref.**
Human periodontal ligament stem cells	Reduces mineralization and ALP activity, and OC; Activates ERK1/2 and JNK	Đorđević et al [137]
Human periodontal ligament stem cells	Reduces ALP activity, and RUNX2, SP7, and OCN expression; Inhibits ERK1/2, p38, and JNK signaling	Jian et al[138]
Murine calvaria progenitor osteoblastic cells	Reduces ALP, mineralization, and nodule formation	Kim et al[139]
Murine-derived BM MSC	IκB kinase-NF-κB dependent catenin degradation	Chang et al [141]
Human bone mesenchymal stem cells	Reduces mineralization; Inhibits RUNX2, ALP, and OPN expression; Wnt inhibition by sFRP1 increased expression	Wang et al [142]
Murine calvaria progenitor osteoblastic cells	Reduces mineralization and ALP activity; Inhibits OC expression; Inhibits Wnt signaling by increasing sFRP1 and suppressing sFRP3 expression	Shaw et al [143]
Murine calvaria progenitor osteoblastic cells	Increases miR-214 and RANKL expression	Liu et al[150]

BM: Bone marrow; MSC: Mesenchymal stem/stromal cell; NF-κB: Nuclear factor-κB; ALP: Alkaline phosphatase; OPN: Osteopontin; OC: Osteocalcin.

periodontal ligament stem cell osteogenic differentiation (by reducing ALP activity, Runx2, SP7, and OCN expression). However, in that case, inhibition of MAPK activation (ERK1,2, p38, and JNK) was involved[138].

IL-17A also inhibits osteogenic differentiation of calvaria osteoblast precursor cells upon chemical induction *in vitro*, as evidenced by reduced ALP expression, mineralization, and nodule formation. Accordingly, IL-17 significantly delayed the *in vivo* filling and repairing calvaria defects[113,139]. Furthermore, NF-κB reduces

osteoblasts' capacity for *in vivo* osteogenic differentiation in a murine periodontal infection model, where IL-17A induced NF-κB transcriptional activity in osteoblasts and osteocytes *in vitro*[140]. Consistent with this, IL-17A inhibits murine MSC osteogenic differentiation *via* IκB kinase (IKK)-NF-κB dependent b-catenin degradation. Moreover, IKK-NF-κB inhibition greatly enhances MSC-mediated bone formation *in vivo*[141]. Consequently, healthy BM-MSCs treated with IL-17 showed impaired osteogenic differentiation when induced with a chemical osteogenic differentiation medium. In addition, IL-17A inhibits Runx2, ALP, and OPN expression and mineralization.

Besides osteogenic inhibition, IL-17 treatment provoked Wnt factor inhibition and increased the Wnt signaling pathway inhibitor sFRP1, a member of the secreted, frizzled-related protein, which mediates IL-17 effects[142]. Similarly, Shaw *et al*[143] demonstrated that IL-17A inhibits calvaria osteoblastic differentiation *in vitro* by inducing sFRP1 and suppressing the expression of sFRP3, a decoy Wnt receptor that may stimulate differentiation through a b-catenin-independent pathway[144]. Interestingly, a study in psoriasis patients indicated that bone loss and low bone formation were correlated with increased serum IL-17A levels. Indeed, two mouse models with chronic IL-17A-mediated skin inflammation showed bone loss and impaired osteoblast activity, whereas keratinocytes, γδT cells, and innate lymphoid cells expressed IL-17A, therefore systemically inhibiting both osteoblast and osteocyte function.

Furthermore, IL-17 treatment *in vivo* and *in vitro* inhibited osteoblast differentiation due to Wnt signaling downregulation, while specific IL-17A blocking antibodies ameliorated bone loss and Wnt signaling[145]. Another potential mechanism linking IL-17A to Wnt signaling reduction could be sclerostin (SOST) upregulation. SOST inhibits the Wnt signaling pathway and bone generation[146]. In coculture conditions, SOST overexpression in adipose-derived MSCs (ADSCs) promoted CD4 T cell differentiation toward Th17 cells expressing IL-17A, concomitantly with ADSCs' impaired osteogenesis and enhanced adipogenic differentiation capacity. Exogenous IL-17A further enhanced ADSCs, overexpressing SOST osteogenic inhibition capacity and promoting adipogenic differentiation[147].

Additionally, IL-17A plays a role in secondary osteoporosis in SLE patients. Human BM-MSCs and SHED transplantation recover bone density and ameliorate structure reduction in MRL/*lpr* mice. The transplantation of human MSCs restores impaired functions and the bone metabolism of recipient mouse BM-MSCs/osteoblasts. The Murine MRL/*lpr* model resembles human SLE disorder, with clinical manifestations due to a Fas^{lpr} mutation that promotes self-reactive lymphocytes' survival[148]. MSCs' effects mainly rely on suppressing abnormal BM IL-17A production in recipient MRL/*lpr* mice, as further confirmed by systemic IL-17A blockage by specific antibodies. The authors suggested two potential mechanisms to explain the MSCs' transplantation effects: MSC integration and differentiation into functional osteoblasts contribute directly to bone regeneration, or proinflammatory cytokines can impair bone regeneration. Therefore, MSCs' anti-inflammatory and immunomodulatory effects may regulate IL-17A production by immune cells at bone defect sites[149].

It has recently been reported that microRNA mir-214 mediates the capacity of IL-17A to inhibit primary murine calvaria osteoblast differentiation *in vitro*[150]. MiR-214 inhibits osteogenesis *in vivo* and *in vitro*[151], and IL-17A increases osteoblast miR-214 production and RANKL expression, promoting osteoclast differentiation in coculture conditions due to the reduction of the OPG/RANKL ratio. Furthermore, knockout miR-214 in osteoblasts decreased *in vivo* osteoclastogenesis. Interestingly, AS patients who manifest bone loss have elevated IL-17A and miR-214 Levels in the serum and synovial fluid, indicating their potential diagnostic value in AS[150].

CONCLUSION

Bone tissue formation and regeneration are highly susceptible to microenvironmental factors that regulate the delicate balance between bone synthesis and resorption. An inflammatory response may influence the proper local cell differentiation after a bone injury to accurately regenerate the tissue. Inflammation precedes bone repair and is crucial for bone healing. As a proinflammatory cytokine, IL-17A is produced at high levels, and its release after bone damage can influence MSCs' fate into early osteoprogenitor/osteoblast cells, which further contributes to bone regeneration and full functional recovery. Despite IL-17's capacity to drive the osteogenic commitment of MSCs, it can also function as an anti-osteogenic factor that causes bone loss. Although

these divergent IL-17A roles in bone formation are still not well understood, various conditions arising from the local microenvironment, the magnitude of inflammation, and the specific nature and stage of osteoprogenitor cells can influence the directionality of IL-17A's function, resulting in specific differentiation outcomes.

From a molecular point of view, it is possible to speculate that two mutually antagonistic signaling pathways in osteogenesis may influence the capacity of IL-17 to function as either a pro-osteogenic or anti-osteogenic factor. In this sense, we hypothesize that, depending on the cell source and culture conditions, the activation of the pro-osteogenic Wnt pathway or the anti-osteogenic NF-κB signaling can regulate the cell decision in response to IL-17[84,152]. Thus, if NF-κB prevails, elevated levels of Wnt inhibitors, sFRPs, and SOTS expression are promoted and may trigger b-catenin degradation, whereby IL-17 is acting as an anti-osteogenic factor. Conversely, if cells exhibit low NF-κB activity, the Wnt pathway can freely operate, and IL-17, in cooperation with this signaling, may function as a pro-osteogenic factor. Accordingly, one potential candidate for controlling NF-κB signaling is IL-10[153], also produced by MSCs[154]. The levels of IL-10 in cell culture may influence NF-κB signaling activity [155] and, thereby, drive IL-17's effect on MSC osteogenic fate. However, this hypothesis needs to be experimentally confirmed.

Moreover, the dual roles of IL-17A might result from species-specific characteristics of MSCs and MSC-derived osteoblasts due to the interplay of various microenvironmental issues that condition IL-17A's effects or mode of action at the cellular level. Although it is clear that IL-17A profoundly affects osteogenic differentiation, further standardized studies are necessary to determine how osteogenic differentiation is either positively or negatively regulated and when IL-17 acts as a pro-osteogenic or anti-osteogenic cytokine. Finally, a deep understanding of the precise inflammatory and tissue conditions may help design better therapeutic strategies for IL-17A-associated bone diseases.

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REFERENCES

1   **Rouvier E**, Luciani MF, Mattéi MG, Denizot F, Golstein P. CTLA-8, cloned from an activated T cell, bearing AU-rich messenger RNA instability sequences, and homologous to a herpesvirus saimiri gene. *J Immunol* 1993; **150**: 5445-5456 [PMID: 8390535]

2   **Yao Z**, Fanslow WC, Seldin MF, Rousseau AM, Painter SL, Comeau MR, Cohen JI, Spriggs MK. Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. *Immunity* 1995; **3**: 811-821 [PMID: 8777726 DOI: 10.1016/1074-7613(95)90070-5]

3   **Park H**, Li Z, Yang XO, Chang SH, Nurieva R, Wang YH, Wang Y, Hood L, Zhu Z, Tian Q, Dong C. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nat Immunol* 2005; **6**: 1133-1141 [PMID: 16200068 DOI: 10.1038/ni1261]

4   **Drescher HK**, Bartsch LM, Weiskirchen S, Weiskirchen R. Intrahepatic T$_H$17/T$_{Reg}$ Cells in Homeostasis and Disease-It's All About the Balance. *Front Pharmacol* 2020; **11**: 588436 [PMID: 33123017 DOI: 10.3389/fphar.2020.588436]

5   **Li X**, Bechara R, Zhao J, McGeachy MJ, Gaffen SL. IL-17 receptor-based signaling and implications for disease. *Nat Immunol* 2019; **20**: 1594-1602 [PMID: 31745337 DOI: 10.1038/s41590-019-0514-y]

6   **Rafael-Vidal C**, Pérez N, Altabás I, Garcia S, Pego-Reigosa JM. Blocking IL-17: A Promising Strategy in the Treatment of Systemic Rheumatic Diseases. *Int J Mol Sci* 2020; **21** [PMID: 32993066 DOI: 10.3390/ijms21197100]

7   **Chamoun MN**, Blumenthal A, Sullivan MJ, Schembri MA, Ulett GC. Bacterial pathogenesis and interleukin-17: interconnecting mechanisms of immune regulation, host genetics, and microbial virulence that influence severity of infection. *Crit Rev Microbiol* 2018; **44**: 465-486 [PMID: 29345518 DOI: 10.1080/1040841X.2018.1426556]

8   **Miossec P**. Local and systemic effects of IL-17 in joint inflammation: a historical perspective from discovery to targeting. *Cell Mol Immunol* 2021; **18**: 860-865 [PMID: 33692481 DOI: 10.1038/s41423-021-00644-5]

9   **Li H**, Chen J, Huang A, Stinson J, Heldens S, Foster J, Dowd P, Gurney AL, Wood WI. Cloning and characterization of IL-17B and IL-17C, two new members of the IL-17 cytokine family. *Proc Natl Acad Sci U S A* 2000; **97**: 773-778 [PMID: 10639155 DOI: 10.1073/pnas.97.2.773]

10   **Starnes T**, Broxmeyer HE, Robertson MJ, Hromas R. Cutting edge: IL-17D, a novel member of the IL-17 family, stimulates cytokine production and inhibits hemopoiesis. *J Immunol* 2002; **169**: 642-646 [PMID: 12097364 DOI: 10.4049/jimmunol.169.2.642]

11   **Benatar T**, Cao MY, Lee Y, Lightfoot J, Feng N, Gu X, Lee V, Jin H, Wang M, Wright JA, Young AH. IL-17E, a proinflammatory cytokine, has antitumor efficacy against several tumor types in vivo. *Cancer Immunol Immunother* 2010; **59**: 805-817 [PMID: 20012860 DOI: 10.1007/s00262-009-0802-8]

12   **Hymowitz SG**, Filvaroff EH, Yin JP, Lee J, Cai L, Risser P, Maruoka M, Mao W, Foster J, Kelley RF, Pan G, Gurney AL, de Vos AM, Starovasnik MA. IL-17s adopt a cystine knot fold: structure and activity of a novel cytokine, IL-17F, and implications for receptor binding. *EMBO J* 2001; **20**: 5332-5341 [PMID: 11574464 DOI: 10.1093/emboj/20.19.5332]

13   **Kostareva OS**, Gabdulkhakov AG, Kolyadenko IA, Garber MB, Tishchenko SV. Interleukin-17: Functional and Structural Features, Application as a Therapeutic Target. *Biochemistry (Mosc)* 2019; **84**: S193-S205 [PMID: 31213202 DOI: 10.1134/S0006297919140116]

14   **Wang X**, Zhang Y, Yang XO, Nurieva RI, Chang SH, Ojeda SS, Kang HS, Schluns KS, Gui J, Jetten AM, Dong C. Transcription of Il17 and Il17f is controlled by conserved noncoding sequence 2. *Immunity* 2012; **36**: 23-31 [PMID: 22244845 DOI: 10.1016/j.immuni.2011.10.019]

15   **Pappu R**, Ramirez-Carrozzi V, Sambandam A. The interleukin-17 cytokine family: critical players in host defence and inflammatory diseases. *Immunology* 2011; **134**: 8-16 [PMID: 21726218 DOI: 10.1111/j.1365-2567.2011.03465.x]

16   **Yao Z**, Spriggs MK, Derry JM, Strockbine L, Park LS, VandenBos T, Zappone JD, Painter SL, Armitage RJ. Molecular characterization of the human interleukin (IL)-17 receptor. *Cytokine* 1997; **9**: 794-800 [PMID: 9367539 DOI: 10.1006/cyto.1997.0240]

17   **Onishi RM**, Gaffen SL. Interleukin-17 and its target genes: mechanisms of interleukin-17 function in disease. *Immunology* 2010; **129**: 311-321 [PMID: 20409152 DOI: 10.1111/j.1365-2567.2009.03240.x]

18   **Gu C**, Wu L, Li X. IL-17 family: cytokines, receptors and signaling. *Cytokine* 2013; **64**: 477-485 [PMID: 24011563 DOI: 10.1016/j.cyto.2013.07.022]

19   **Wu L**, Chen X, Zhao J, Martin B, Zepp JA, Ko JS, Gu C, Cai G, Ouyang W, Sen G, Stark GR, Su B, Vines CM, Tournier C, Hamilton TA, Vidimos A, Gastman B, Liu C, Li X. A novel IL-17 signaling pathway controlling keratinocyte proliferation and tumorigenesis *via* the TRAF4-ERK5 axis. *J Exp Med* 2015; **212**: 1571-1587 [PMID: 26347473 DOI: 10.1084/jem.20150204]

20   **Amatya N**, Garg AV, Gaffen SL. IL-17 Signaling: The Yin and the Yang. *Trends Immunol* 2017; **38**: 310-322 [PMID: 28254169 DOI: 10.1016/j.it.2017.01.006]

21   **Friedenstein AJ**. Precursor cells of mechanocytes. *Int Rev Cytol* 1976; **47**: 327-359 [PMID: 11195 DOI: 10.1016/s0074-7696(08)60092-3]

22   **Friedenstein AJ**, Chailakhyan RK, Latsinik NV, Panasyuk AF, Keiliss-Borok IV. Stromal cells responsible for transferring the microenvironment of the hemopoietic tissues. Cloning *in vitro* and retransplantation in vivo. *Transplantation* 1974; **17**: 331-340 [PMID: 4150881 DOI: 10.1097/00007890-197404000-00001]

23   **Friedenstein AJ**, Piatetzky-Shapiro II, Petrakova KV. Osteogenesis in transplants of bone marrow cells. *J Embryol Exp Morphol* 1966; **16**: 381-390 [PMID: 5336210]

24   **Robert AW**, Marcon BH, Dallagiovanna B, Shigunov P. Adipogenesis, Osteogenesis, and Chondrogenesis of Human Mesenchymal Stem/Stromal Cells: A Comparative Transcriptome Approach. *Front Cell Dev Biol* 2020; **8**: 561 [PMID: 32733882 DOI: 10.3389/fcell.2020.00561]

25   **Dominici M**, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop Dj, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* 2006; **8**: 315-317 [PMID: 16923606 DOI: 10.1080/14653240600855905]

26   **Arthur A**, Gronthos S. Clinical Application of Bone Marrow Mesenchymal Stem/Stromal Cells to Repair Skeletal Tissue. *Int J Mol Sci* 2020; **21** [PMID: 33371306 DOI: 10.3390/ijms21249759]

27   **da Silva Meirelles L**, Chagastelles PC, Nardi NB. Mesenchymal stem cells reside in virtually all post-natal organs and tissues. *J Cell Sci* 2006; **119**: 2204-2213 [PMID: 16684817 DOI: 10.1242/jcs.02932]

28   **Gan L**, Liu Y, Cui D, Pan Y, Zheng L, Wan M. Dental Tissue-Derived Human Mesenchymal Stem Cells and Their Potential in Therapeutic Application. *Stem Cells Int* 2020; **2020**: 8864572 [PMID: 32952572 DOI: 10.1155/2020/8864572]

29   **Hutchings G**, Moncrieff L, Dompe C, Janowicz K, Sibiak R, Bryja A, Jankowski M, Mozdziak P, Bukowska D, Antosik P, Shibli JA, Dyszkiewicz-Konwińska M, Bruska M, Kempisty B, Piotrowska-Kempisty H. Bone Regeneration, Reconstruction and Use of Osteogenic Cells; from Basic Knowledge, Animal Models to Clinical Trials. *J Clin Med* 2020; **9** [PMID: 31947922 DOI: 10.3390/jcm9010139]

30   **Levy O**, Kuai R, Siren EMJ, Bhere D, Milton Y, Nissar N, De Biasio M, Heinelt M, Reeve B, Abdi R, Alturki M, Fallatah M, Almalik A, Alhasan AH, Shah K, Karp JM. Shattering barriers toward clinically meaningful MSC therapies. *Sci Adv* 2020; **6**: eaba6884 [PMID: 32832666 DOI: 10.1126/sciadv.aba6884]

31   **Stamnitz S**, Klimczak A. Mesenchymal Stem Cells, Bioactive Factors, and Scaffolds in Bone Repair: From Research Perspectives to Clinical Practice. *Cells* 2021; **10** [PMID: 34440694 DOI: 10.3390/cells10081925]

32   **Merimi M**, El-Majzoub R, Lagneaux L, Moussa Agha D, Bouhtit F, Meuleman N, Fahmi H, Lewalle P, Fayyad-Kazan M, Najar M. The Therapeutic Potential of Mesenchymal Stromal Cells for Regenerative Medicine: Current Knowledge and Future Understandings. *Front Cell Dev Biol* 2021; **9**: 661532 [PMID: 34490235 DOI: 10.3389/fcell.2021.661532]

33   **Qiao Y**, Agboola OS, Hu X, Wu Y, Lei L. Tumorigenic and Immunogenic Properties of Induced Pluripotent Stem Cells: a Promising Cancer Vaccine. *Stem Cell Rev Rep* 2020; **16**: 1049-1061 [PMID: 32939647 DOI: 10.1007/s12015-020-10042-5]

34   **Yasuda S**, Kusakawa S, Kuroda T, Miura T, Tano K, Takada N, Matsuyama S, Matsuyama A, Nasu M, Umezawa A, Hayakawa T, Tsutsumi H, Sato Y. Tumorigenicity-associated characteristics of human iPS cell lines. *PLoS One* 2018; **13**: e0205022 [PMID: 30286143 DOI: 10.1371/journal.pone.0205022]

35   **Ankrum JA**, Ong JF, Karp JM. Mesenchymal stem cells: immune evasive, not immune privileged. *Nat Biotechnol* 2014; **32**: 252-260 [PMID: 24561556 DOI: 10.1038/nbt.2816]

36   **Lou S**, Duan Y, Nie H, Cui X, Du J, Yao Y. Mesenchymal stem cells: Biological characteristics and application in disease therapy. *Biochimie* 2021; **185**: 9-21 [PMID: 33711361 DOI: 10.1016/j.biochi.2021.03.003]

37   **Mezey É**, Nemeth K. Mesenchymal stem cells and infectious diseases: Smarter than drugs. *Immunol Lett* 2015; **168**: 208-214 [PMID: 26051681 DOI: 10.1016/j.imlet.2015.05.020]

38   **Shang F**, Yu Y, Liu S, Ming L, Zhang Y, Zhou Z, Zhao J, Jin Y. Advancing application of mesenchymal stem cell-based bone tissue regeneration. *Bioact Mater* 2021; **6**: 666-683 [PMID: 33005830 DOI: 10.1016/j.bioactmat.2020.08.014]

39   **Munir H**, Ward LSC, McGettrick HM. Mesenchymal Stem Cells as Endogenous Regulators of Inflammation. *Adv Exp Med Biol* 2018; **1060**: 73-98 [PMID: 30155623 DOI: 10.1007/978-3-319-78127-3_5]

40   **Goodman SB**, Lin T. Modifying MSC Phenotype to Facilitate Bone Healing: Biological Approaches. *Front Bioeng Biotechnol* 2020; **8**: 641 [PMID: 32671040 DOI: 10.3389/fbioe.2020.00641]

41   **Bryniarska N**, Kubiak A, Łabędź-Masłowska A, Zuba-Surma E. Impact of developmental origin, niche mechanics and oxygen availability on osteogenic differentiation capacity of mesenchymal stem/stromal cells. *Acta Biochim Pol* 2019; **66**: 491-498 [PMID: 31883439 DOI: 10.18388/abp.2019_2893]

42   **Oryan A**, Monazzah S, Bigham-Sadegh A. Bone injury and fracture healing biology. *Biomed Environ Sci* 2015; **28**: 57-71 [PMID: 25566863 DOI: 10.3967/bes2015.006]

43   **Kurenkova AD**, Medvedeva EV, Newton PT, Chagin AS. Niches for Skeletal Stem Cells of Mesenchymal Origin. *Front Cell Dev Biol* 2020; **8**: 592 [PMID: 32754592 DOI: 10.3389/fcell.2020.00592]

44   **Viguet-Carrin S**, Garnero P, Delmas PD. The role of collagen in bone strength. *Osteoporos Int* 2006; **17**: 319-336 [PMID: 16341622 DOI: 10.1007/s00198-005-2035-9]

45   **Florencio-Silva R**, Sasso GR, Sasso-Cerri E, Simões MJ, Cerri PS. Biology of Bone Tissue: Structure, Function, and Factors That Influence Bone Cells. *Biomed Res Int* 2015; **2015**: 421746 [PMID: 26247020 DOI: 10.1155/2015/421746]

46   **Jeong J**, Kim JH, Shim JH, Hwang NS, Heo CY. Bioactive calcium phosphate materials and applications in bone regeneration. *Biomater Res* 2019; **23**: 4 [PMID: 30675377 DOI: 10.1186/s40824-018-0149-3]

47   **Mohamed AM**. An overview of bone cells and their regulating factors of differentiation. *Malays J Med Sci* 2008; **15**: 4-12 [PMID: 22589609]

48   **Le BQ**, Nurcombe V, Cool SM, van Blitterswijk CA, de Boer J, LaPointe VLS. The Components of Bone and What They Can Teach Us about Regeneration. *Materials (Basel)* 2017; **11** [PMID: 29271933 DOI: 10.3390/ma11010014]

49   **Granero-Moltó F**, Weis JA, Miga MI, Landis B, Myers TJ, O'Rear L, Longobardi L, Jansen ED, Mortlock DP, Spagnoli A. Regenerative effects of transplanted mesenchymal stem cells in fracture healing. *Stem Cells* 2009; **27**: 1887-1898 [PMID: 19544445 DOI: 10.1002/stem.103]

50   **Atkins GJ**, Findlay DM. Osteocyte regulation of bone mineral: a little give and take. *Osteoporos Int* 2012; **23**: 2067-2079 [PMID: 22302104 DOI: 10.1007/s00198-012-1915-z]

51   **Creecy A**, Damrath JG, Wallace JM. Control of Bone Matrix Properties by Osteocytes. *Front Endocrinol (Lausanne)* 2020; **11**: 578477 [PMID: 33537002 DOI: 10.3389/fendo.2020.578477]

52   **Schaffler MB**, Cheung WY, Majeska R, Kennedy O. Osteocytes: master orchestrators of bone. *Calcif Tissue Int* 2014; **94**: 5-24 [PMID: 24042263 DOI: 10.1007/s00223-013-9790-y]

53   **Cao W**, Helder MN, Bravenboer N, Wu G, Jin J, Ten Bruggenkate CM, Klein-Nulend J, Schulten EAJM. Is There a Governing Role of Osteocytes in Bone Tissue Regeneration? *Curr Osteoporos Rep* 2020; **18**: 541-550 [PMID: 32676786 DOI: 10.1007/s11914-020-00610-6]

54   **Infante A**, Rodríguez CI. Osteogenesis and aging: lessons from mesenchymal stem cells. *Stem Cell Res Ther* 2018; **9**: 244 [PMID: 30257716 DOI: 10.1186/s13287-018-0995-x]

55   **Shah FA**, Thomsen P, Palmquist A. A Review of the Impact of Implant Biomaterials on Osteocytes. *J Dent Res* 2018; **97**: 977-986 [PMID: 29863948 DOI: 10.1177/0022034518778033]

56   **Khan IA**, Bordoni B. Histology, Osteoclasts. 2021 Apr 28. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan- [PMID: 32119376]

57   **Kitaura H**, Marahleh A, Ohori F, Noguchi T, Shen WR, Qi J, Nara Y, Pramusita A, Kinjo R, Mizoguchi I. Osteocyte-Related Cytokines Regulate Osteoclast Formation and Bone Resorption. *Int*

J Mol Sci 2020; **21** [PMID: 32708317 DOI: 10.3390/ijms21145169]

58   **Berendsen AD**, Olsen BR. Bone development. *Bone* 2015; **80**: 14-18 [PMID: 26453494 DOI: 10.1016/j.bone.2015.04.035]

59   **Wang Y**, Li YP, Paulson C, Shao JZ, Zhang X, Wu M, Chen W. Wnt and the Wnt signaling pathway in bone development and disease. *Front Biosci (Landmark Ed)* 2014; **19**: 379-407 [PMID: 24389191 DOI: 10.2741/4214]

60   **Chen Q**, Shou P, Zheng C, Jiang M, Cao G, Yang Q, Cao J, Xie N, Velletri T, Zhang X, Xu C, Zhang L, Yang H, Hou J, Wang Y, Shi Y. Fate decision of mesenchymal stem cells: adipocytes or osteoblasts? *Cell Death Differ* 2016; **23**: 1128-1139 [PMID: 26868907 DOI: 10.1038/cdd.2015.168]

61   **Kokabu S**, Lowery JW, Jimi E. Cell Fate and Differentiation of Bone Marrow Mesenchymal Stem Cells. *Stem Cells Int* 2016; **2016**: 3753581 [PMID: 27298623 DOI: 10.1155/2016/3753581]

62   **Pierce JL**, Begun DL, Westendorf JJ, McGee-Lawrence ME. Defining osteoblast and adipocyte lineages in the bone marrow. *Bone* 2019; **118**: 2-7 [PMID: 29782940 DOI: 10.1016/j.bone.2018.05.019]

63   **Stains JP**, Civitelli R. Genomic approaches to identifying transcriptional regulators of osteoblast differentiation. *Genome Biol* 2003; **4**: 222 [PMID: 12844353 DOI: 10.1186/gb-2003-4-7-222]

64   **Ducy P**. Cbfa1: a molecular switch in osteoblast biology. *Dev Dyn* 2000; **219**: 461-471 [PMID: 11084646 DOI: 10.1002/1097-0177(2000)9999:9999<::AID-DVDY1074>3.0.CO;2-C]

65   **Franceschi RT**, Xiao G, Jiang D, Gopalakrishnan R, Yang S, Reith E. Multiple signaling pathways converge on the Cbfa1/Runx2 transcription factor to regulate osteoblast differentiation. *Connect Tissue Res* 2003; **44** Suppl 1: 109-116 [PMID: 12952183]

66   **Shetty S**, Kapoor N, Bondu JD, Thomas N, Paul TV. Bone turnover markers: Emerging tool in the management of osteoporosis. *Indian J Endocrinol Metab* 2016; **20**: 846-852 [PMID: 27867890 DOI: 10.4103/2230-8210.192914]

67   **Frith J**, Genever P. Transcriptional control of mesenchymal stem cell differentiation. *Transfus Med Hemother* 2008; **35**: 216-227 [PMID: 21547119]

68   **Denhardt DT**, Noda M. Osteopontin expression and function: role in bone remodeling. *J Cell Biochem Suppl* 1998; **30-31**: 92-102 [PMID: 9893260]

69   **Klein-Nulend J**, Roelofsen J, Semeins CM, Bronckers AL, Burger EH. Mechanical stimulation of osteopontin mRNA expression and synthesis in bone cell cultures. *J Cell Physiol* 1997; **170**: 174-181 [PMID: 9009146 DOI: 10.1002/(SICI)1097-4652(199702)170:2<174::AID-JCP9>3.0.CO;2-L]

70   **Simonet WS**, Lacey DL, Dunstan CR, Kelley M, Chang MS, Lüthy R, Nguyen HQ, Wooden S, Bennett L, Boone T, Shimamoto G, DeRose M, Elliott R, Colombero A, Tan HL, Trail G, Sullivan J, Davy E, Bucay N, Renshaw-Gegg L, Hughes TM, Hill D, Pattison W, Campbell P, Sander S, Van G, Tarpley J, Derby P, Lee R, Boyle WJ. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. *Cell* 1997; **89**: 309-319 [PMID: 9108485 DOI: 10.1016/s0092-8674(00)80209-3]

71   **Tsuda E**, Goto M, Mochizuki S, Yano K, Kobayashi F, Morinaga T, Higashio K. Isolation of a novel cytokine from human fibroblasts that specifically inhibits osteoclastogenesis. *Biochem Biophys Res Commun* 1997; **234**: 137-142 [PMID: 9168977 DOI: 10.1006/bbrc.1997.6603]

72   **Infante M**, Fabi A, Cognetti F, Gorini S, Caprio M, Fabbri A. RANKL/RANK/OPG system beyond bone remodeling: involvement in breast cancer and clinical perspectives. *J Exp Clin Cancer Res* 2019; **38**: 12 [PMID: 30621730 DOI: 10.1186/s13046-018-1001-2]

73   **Rosset EM**, Bradshaw AD. SPARC/osteonectin in mineralized tissue. *Matrix Biol* 2016; **52-54**: 78-87 [PMID: 26851678 DOI: 10.1016/j.matbio.2016.02.001]

74   **Ducy P**, Desbois C, Boyce B, Pinero G, Story B, Dunstan C, Smith E, Bonadio J, Goldstein S, Gundberg C, Bradley A, Karsenty G. Increased bone formation in osteocalcin-deficient mice. *Nature* 1996; **382**: 448-452 [PMID: 8684484 DOI: 10.1038/382448a0]

75   **Si J**, Wang C, Zhang D, Wang B, Zhou Y. Osteopontin in Bone Metabolism and Bone Diseases. *Med Sci Monit* 2020; **26**: e919159 [PMID: 31996665 DOI: 10.12659/MSM.919159]

76   **James AW**. Review of Signaling Pathways Governing MSC Osteogenic and Adipogenic Differentiation. *Scientifica (Cairo)* 2013; **2013**: 684736 [PMID: 24416618 DOI: 10.1155/2013/684736]

77   **Day TF**, Guo X, Garrett-Beal L, Yang Y. Wnt/beta-catenin signaling in mesenchymal progenitors controls osteoblast and chondrocyte differentiation during vertebrate skeletogenesis. *Dev Cell* 2005; **8**: 739-750 [PMID: 15866164 DOI: 10.1016/j.devcel.2005.03.016]

78   **Moorer MC**, Riddle RC. Regulation of Osteoblast Metabolism by Wnt Signaling. *Endocrinol Metab (Seoul)* 2018; **33**: 318-330 [PMID: 30112869 DOI: 10.3803/EnM.2018.33.3.318]

79   **Ge L**, Cui Y, Liu B, Yin X, Pang J, Han J. ERα and Wnt/βcatenin signaling pathways are involved in angelicindependent promotion of osteogenesis. *Mol Med Rep* 2019; **19**: 3469-3476 [PMID: 30864714 DOI: 10.3892/mmr.2019.9999]

80   **Kang S**, Bennett CN, Gerin I, Rapp LA, Hankenson KD, Macdougald OA. Wnt signaling stimulates osteoblastogenesis of mesenchymal precursors by suppressing CCAAT/enhancer-binding protein alpha and peroxisome proliferator-activated receptor gamma. *J Biol Chem* 2007; **282**: 14515-14524 [PMID: 17351296 DOI: 10.1074/jbc.M700030200]

81   **Williams BO**, Insogna KL. Where Wnts went: the exploding field of Lrp5 and Lrp6 signaling in bone. *J Bone Miner Res* 2009; **24**: 171-178 [PMID: 19072724 DOI: 10.1359/jbmr.081235]

82   **Honma M**, Ikebuchi Y, Kariya Y, Suzuki H. Regulatory mechanisms of RANKL presentation to osteoclast precursors. *Curr Osteoporos Rep* 2014; **12**: 115-120 [PMID: 24477414 DOI:

10.1007/s11914-014-0189-0]

83   **Xu C**, Wang J, Zhu T, Shen Y, Tang X, Fang L, Xu Y. Cross-Talking Between PPAR and WNT Signaling and its Regulation in Mesenchymal Stem Cell Differentiation. *Curr Stem Cell Res Ther* 2016; **11**: 247-254 [PMID: 26201865 DOI: 10.2174/1574888x10666150723145707]

84   **Ling L**, Nurcombe V, Cool SM. Wnt signaling controls the fate of mesenchymal stem cells. *Gene* 2009; **433**: 1-7 [PMID: 19135507 DOI: 10.1016/j.gene.2008.12.008]

85   **Nickel J**, Mueller TD. Specification of BMP Signaling. *Cells* 2019; **8** [PMID: 31817503 DOI: 10.3390/cells8121579]

86   **Wu M**, Chen G, Li YP. TGF-β and BMP signaling in osteoblast, skeletal development, and bone formation, homeostasis and disease. *Bone Res* 2016; **4**: 16009 [PMID: 27563484 DOI: 10.1038/boneres.2016.9]

87   **Maeda Y**, Tsuji K, Nifuji A, Noda M. Inhibitory helix-loop-helix transcription factors Id1/Id3 promote bone formation in vivo. *J Cell Biochem* 2004; **93**: 337-344 [PMID: 15368360 DOI: 10.1002/jcb.20154]

88   **Lowery JW**, Rosen V. The BMP Pathway and Its Inhibitors in the Skeleton. *Physiol Rev* 2018; **98**: 2431-2452 [PMID: 30156494 DOI: 10.1152/physrev.00028.2017]

89   **Abdelmagid SM**, Barbe MF, Rico MC, Salihoglu S, Arango-Hisijara I, Selim AH, Anderson MG, Owen TA, Popoff SN, Safadi FF. Osteoactivin, an anabolic factor that regulates osteoblast differentiation and function. *Exp Cell Res* 2008; **314**: 2334-2351 [PMID: 18555216 DOI: 10.1016/j.yexcr.2008.02.006]

90   **Wang Q**, Wei X, Zhu T, Zhang M, Shen R, Xing L, O'Keefe RJ, Chen D. Bone morphogenetic protein 2 activates Smad6 gene transcription through bone-specific transcription factor Runx2. *J Biol Chem* 2007; **282**: 10742-10748 [PMID: 17215250 DOI: 10.1074/jbc.M610997200]

91   **Jaiswal RK**, Jaiswal N, Bruder SP, Mbalaviele G, Marshak DR, Pittenger MF. Adult human mesenchymal stem cell differentiation to the osteogenic or adipogenic lineage is regulated by mitogen-activated protein kinase. *J Biol Chem* 2000; **275**: 9645-9652 [PMID: 10734116 DOI: 10.1074/jbc.275.13.9645]

92   **Ono T**, Takayanagi H. Osteoimmunology in Bone Fracture Healing. *Curr Osteoporos Rep* 2017; **15**: 367-375 [PMID: 28647888 DOI: 10.1007/s11914-017-0381-0]

93   **Takayanagi H**. Osteoimmunology and the effects of the immune system on bone. *Nat Rev Rheumatol* 2009; **5**: 667-676 [PMID: 19884898 DOI: 10.1038/nrrheum.2009.217]

94   **Komatsu N**, Takayanagi H. Inflammation and bone destruction in arthritis: synergistic activity of immune and mesenchymal cells in joints. *Front Immunol* 2012; **3**: 77 [PMID: 22566958 DOI: 10.3389/fimmu.2012.00077]

95   **Mojsilović S**, Jauković A, Santibañez JF, Bugarski D. Interleukin-17 and its implication in the regulation of differentiation and function of hematopoietic and mesenchymal stem cells. *Mediators Inflamm* 2015; **2015**: 470458 [PMID: 25999667 DOI: 10.1155/2015/470458]

96   **Le Goff B**, Bouvard B, Lequerre T, Lespessailles E, Marotte H, Pers YM, Cortet B. Implication of IL-17 in Bone Loss and Structural Damage in Inflammatory Rheumatic Diseases. *Mediators Inflamm* 2019; **2019**: 8659302 [PMID: 31485194 DOI: 10.1155/2019/8659302]

97   **Huang H**, Kim HJ, Chang EJ, Lee ZH, Hwang SJ, Kim HM, Lee Y, Kim HH. IL-17 stimulates the proliferation and differentiation of human mesenchymal stem cells: implications for bone remodeling. *Cell Death Differ* 2009; **16**: 1332-1343 [PMID: 19543237 DOI: 10.1038/cdd.2009.74]

98   **Huang W**, La Russa V, Alzoubi A, Schwarzenberger P. Interleukin-17A: a T-cell-derived growth factor for murine and human mesenchymal stem cells. *Stem Cells* 2006; **24**: 1512-1518 [PMID: 16513762 DOI: 10.1634/stemcells.2005-0156]

99   **Mojsilović S**, Krstić A, Ilić V, Okić-Đorđević I, Kocić J, Trivanović D, Santibañez JF, Jovčić G, Bugarski D. IL-17 and FGF signaling involved in mouse mesenchymal stem cell proliferation. *Cell Tissue Res* 2011; **346**: 305-316 [PMID: 22160457 DOI: 10.1007/s00441-011-1284-5]

100   **Krstić J**, Obradović H, Jauković A, Okić-Đorđević I, Trivanović D, Kukolj T, Mojsilović S, Ilić V, Santibañez JF, Bugarski D. Urokinase type plasminogen activator mediates Interleukin-17-induced peripheral blood mesenchymal stem cell motility and transendothelial migration. *Biochim Biophys Acta* 2015; **1853**: 431-444 [PMID: 25433194 DOI: 10.1016/j.bbamcr.2014.11.025]

101   **Sivanathan KN**, Rojas-Canales D, Grey ST, Gronthos S, Coates PT. Transcriptome Profiling of IL-17A Preactivated Mesenchymal Stem Cells: A Comparative Study to Unmodified and IFN-γ Modified Mesenchymal Stem Cells. *Stem Cells Int* 2017; **2017**: 1025820 [PMID: 28293262 DOI: 10.1155/2017/1025820]

102   **Wang S**, Wang G, Zhang L, Li F, Liu K, Wang Y, Shi Y, Cao K. Interleukin-17 promotes nitric oxide-dependent expression of PD-L1 in mesenchymal stem cells. *Cell Biosci* 2020; **10**: 73 [PMID: 32509271 DOI: 10.1186/s13578-020-00431-1]

103   **Han X**, Yang Q, Lin L, Xu C, Zheng C, Chen X, Han Y, Li M, Cao W, Cao K, Chen Q, Xu G, Zhang Y, Zhang J, Schneider RJ, Qian Y, Wang Y, Brewer G, Shi Y. Interleukin-17 enhances immunosuppression by mesenchymal stem cells. *Cell Death Differ* 2014; **21**: 1758-1768 [PMID: 25034782 DOI: 10.1038/cdd.2014.85]

104   **Sivanathan KN**, Rojas-Canales DM, Hope CM, Krishnan R, Carroll RP, Gronthos S, Grey ST, Coates PT. Interleukin-17A-Induced Human Mesenchymal Stem Cells Are Superior Modulators of Immunological Function. *Stem Cells* 2015; **33**: 2850-2863 [PMID: 26037953 DOI: 10.1002/stem.2075]

105   **Waterman RS**, Tomchuck SL, Henkle SL, Betancourt AM. A new mesenchymal stem cell (MSC)

paradigm: polarization into a pro-inflammatory MSC1 or an Immunosuppressive MSC2 phenotype. *PLoS One* 2010; **5**: e10088 [PMID: 20436665 DOI: 10.1371/journal.pone.0010088]

106   **He T**, Huang Y, Zhang C, Liu D, Cheng C, Xu W, Zhang X. Interleukin-17A-promoted MSC2 polarization related with new bone formation of ankylosing spondylitis. *Oncotarget* 2017; **8**: 96993-97008 [PMID: 29228588 DOI: 10.18632/oncotarget.20823]

107   **Liao C**, Zhang C, Jin L, Yang Y. IL-17 alters the mesenchymal stem cell niche towards osteogenesis in cooperation with osteocytes. *J Cell Physiol* 2020; **235**: 4466-4480 [PMID: 31643095 DOI: 10.1002/jcp.29323]

108   **Jo S**, Lee JK, Han J, Lee B, Kang S, Hwang KT, Park YS, Kim TH. Identification and characterization of human bone-derived cells. *Biochem Biophys Res Commun* 2018; **495**: 1257-1263 [PMID: 29180008 DOI: 10.1016/j.bbrc.2017.11.155]

109   **Jo S**, Wang SE, Lee YL, Kang S, Lee B, Han J, Sung IH, Park YS, Bae SC, Kim TH. IL-17A induces osteoblast differentiation by activating JAK2/STAT3 in ankylosing spondylitis. *Arthritis Res Ther* 2018; **20**: 115 [PMID: 29880011 DOI: 10.1186/s13075-018-1582-3]

110   **Shah M**, Maroof A, Gikas P, Mittal G, Keen R, Baeten D, Shaw S, Roberts SJ. Dual neutralisation of IL-17F and IL-17A with bimekizumab blocks inflammation-driven osteogenic differentiation of human periosteal cells. *RMD Open* 2020; **6** [PMID: 32723833 DOI: 10.1136/rmdopen-2020-001306]

111   **Sethi N**. The significance of osteitis in rhinosinusitis. *Eur Arch Otorhinolaryngol* 2015; **272**: 821-826 [PMID: 24771214 DOI: 10.1007/s00405-014-3060-0]

112   **Khalmuratova R**, Shin HW, Kim DW, Park JW. Interleukin (IL)-13 and IL-17A contribute to neo-osteogenesis in chronic rhinosinusitis by inducing RUNX2. *EBioMedicine* 2019; **46**: 330-341 [PMID: 31331833 DOI: 10.1016/j.ebiom.2019.07.035]

113   **Ono T**, Okamoto K, Nakashima T, Nitta T, Hori S, Iwakura Y, Takayanagi H. IL-17-producing γδ T cells enhance bone regeneration. *Nat Commun* 2016; **7**: 10928 [PMID: 26965320 DOI: 10.1038/ncomms10928]

114   **Croes M**, Öner FC, van Neerven D, Sabir E, Kruyt MC, Blokhuis TJ, Dhert WJA, Alblas J. Proinflammatory T cells and IL-17 stimulate osteoblast differentiation. *Bone* 2016; **84**: 262-270 [PMID: 26780388 DOI: 10.1016/j.bone.2016.01.010]

115   **Croes M**, Kruyt MC, Groen WM, van Dorenmalen KMA, Dhert WJA, Öner FC, Alblas J. Interleukin 17 enhances bone morphogenetic protein-2-induced ectopic bone formation. *Sci Rep* 2018; **8**: 7269 [PMID: 29740080 DOI: 10.1038/s41598-018-25564-9]

116   **Zheng C**, Chen J, Liu S, Jin Y. Stem cell-based bone and dental regeneration: a view of microenvironmental modulation. *Int J Oral Sci* 2019; **11**: 23 [PMID: 31423011 DOI: 10.1038/s41368-019-0060-3]

117   **Yu W**, Zhang Y, Jiang C, He W, Yi Y, Wang J. Orthodontic treatment mediates dental pulp microenvironment *via* IL17A. *Arch Oral Biol* 2016; **66**: 22-29 [PMID: 26874428 DOI: 10.1016/j.archoralbio.2016.01.009]

118   **Sebastian AA**, Kannan TP, Norazmi MN, Nurul AA. Interleukin-17A promotes osteogenic differentiation by increasing OPG/RANKL ratio in stem cells from human exfoliated deciduous teeth (SHED). *J Tissue Eng Regen Med* 2018; **12**: 1856-1866 [PMID: 29774992 DOI: 10.1002/term.2706]

119   **Wang Z**, Wei Y, Lei L, Zhong J, Shen Y, Tan J, Xia M, Wu Y, Sun W, Chen L. RANKL expression of primary osteoblasts is enhanced by an IL-17-mediated JAK2/STAT3 pathway through autophagy suppression. *Connect Tissue Res* 2021; **62**: 411-426 [PMID: 32370570 DOI: 10.1080/03008207.2020.1759562]

120   **Jones DC**, Wein MN, Glimcher LH. Schnurri-3: a key regulator of postnatal skeletal remodeling. *Adv Exp Med Biol* 2007; **602**: 1-13 [PMID: 17966382 DOI: 10.1007/978-0-387-72009-8_1]

121   **Osta B**, Lavocat F, Eljaafari A, Miossec P. Effects of Interleukin-17A on Osteogenic Differentiation of Isolated Human Mesenchymal Stem Cells. *Front Immunol* 2014; **5**: 425 [PMID: 25228904 DOI: 10.3389/fimmu.2014.00425]

122   **Auréal M**, Machuca-Gayet I, Coury F. Rheumatoid Arthritis in the View of Osteoimmunology. *Biomolecules* 2020; **11** [PMID: 33396412 DOI: 10.3390/biom11010048]

123   **Di Nicola V**. Degenerative osteoarthritis a reversible chronic disease. *Regen Ther* 2020; **15**: 149-160 [PMID: 33426213 DOI: 10.1016/j.reth.2020.07.007]

124   **Bustamante MF**, Garcia-Carbonell R, Whisenant KD, Guma M. Fibroblast-like synoviocyte metabolism in the pathogenesis of rheumatoid arthritis. *Arthritis Res Ther* 2017; **19**: 110 [PMID: 28569176 DOI: 10.1186/s13075-017-1303-3]

125   **Osta B**, Roux JP, Lavocat F, Pierre M, Ndongo-Thiam N, Boivin G, Miossec P. Differential Effects of IL-17A and TNF-α on Osteoblastic Differentiation of Isolated Synoviocytes and on Bone Explants from Arthritis Patients. *Front Immunol* 2015; **6**: 151 [PMID: 25904914 DOI: 10.3389/fimmu.2015.00151]

126   **Kocić J**, Santibañez JF, Krstić A, Mojsilović S, Đorđević IO, Trivanović D, Ilić V, Bugarski D. Interleukin 17 inhibits myogenic and promotes osteogenic differentiation of C2C12 myoblasts by activating ERK1,2. *Biochim Biophys Acta* 2012; **1823**: 838-849 [PMID: 22285818 DOI: 10.1016/j.bbamcr.2012.01.001]

127   **Kocić J**, Santibañez JF, Krstić A, Mojsilović S, Ilić V, Bugarski D. Interleukin-17 modulates myoblast cell migration by inhibiting urokinase type plasminogen activator expression through p38 mitogen-activated protein kinase. *Int J Biochem Cell Biol* 2013; **45**: 464-475 [PMID: 23183001

DOI: 10.1016/j.biocel.2012.11.010]

128   **Kim HJ**, Seo SJ, Kim JY, Kim YG, Lee Y. IL-17 promotes osteoblast differentiation, bone regeneration, and remodeling in mice. *Biochem Biophys Res Commun* 2020; **524**: 1044-1050 [PMID: 32067737 DOI: 10.1016/j.bbrc.2020.02.054]

129   **Sudo H**, Kodama HA, Amagai Y, Yamamoto S, Kasai S. In vitro differentiation and calcification in a new clonal osteogenic cell line derived from newborn mouse calvaria. *J Cell Biol* 1983; **96**: 191-198 [PMID: 6826647 DOI: 10.1083/jcb.96.1.191]

130   **Tan JY**, Lei LH, Chen XT, Ding PH, Wu YM, Chen LL. AKT2 is involved in the IL17Amediated promotion of differentiation and calcification of murine preosteoblastic MC3T3E1 cells. *Mol Med Rep* 2017; **16**: 5833-5840 [PMID: 28849233 DOI: 10.3892/mmr.2017.7315]

131   **Sritharan S**, Kannan TP, Norazmi MN, Nurul AA. The synergistic effects of IL-6/IL-17A promote osteogenic differentiation by improving OPG/RANKL ratio and adhesion of MC3T3-E1 cells on hydroxyapatite. *J Craniomaxillofac Surg* 2018; **46**: 1361-1367 [PMID: 29805067 DOI: 10.1016/j.jcms.2018.05.002]

132   **Russell T**, Bridgewood C, Rowe H, Altaie A, Jones E, McGonagle D. Cytokine "fine tuning" of enthesis tissue homeostasis as a pointer to spondyloarthritis pathogenesis with a focus on relevant TNF and IL-17 targeted therapies. *Semin Immunopathol* 2021; **43**: 193-206 [PMID: 33544244 DOI: 10.1007/s00281-021-00836-1]

133   **Shin JH**, Shin DW, Noh M. Interleukin-17A inhibits adipocyte differentiation in human mesenchymal stem cells and regulates pro-inflammatory responses in adipocytes. *Biochem Pharmacol* 2009; **77**: 1835-1844 [PMID: 19428338 DOI: 10.1016/j.bcp.2009.03.008]

134   **Noh M**. Interleukin-17A increases leptin production in human bone marrow mesenchymal stem cells. *Biochem Pharmacol* 2012; **83**: 661-670 [PMID: 22197587 DOI: 10.1016/j.bcp.2011.12.010]

135   **Ahmed M**, Gaffen SL. IL-17 inhibits adipogenesis in part *via* C/EBPα, PPARγ and Krüppel-like factors. *Cytokine* 2013; **61**: 898-905 [PMID: 23332504 DOI: 10.1016/j.cyto.2012.12.007]

136   **Kondo M**, Yamaoka K, Sonomoto K, Fukuyo S, Oshita K, Okada Y, Tanaka Y. IL-17 inhibits chondrogenic differentiation of human mesenchymal stem cells. *PLoS One* 2013; **8**: e79463 [PMID: 24260226 DOI: 10.1371/journal.pone.0079463]

137   **Đorđević IO**, Kukolj T, Krstić J, Trivanović D, Obradović H, Santibañez JF, Mojsilović S, Ilić V, Bugarski D, Jauković A. The inhibition of periodontal ligament stem cells osteogenic differentiation by IL-17 is mediated *via* MAPKs. *Int J Biochem Cell Biol* 2016; **71**: 92-101 [PMID: 26718973 DOI: 10.1016/j.biocel.2015.12.007]

138   **Jian CX**, Fan QS, Hu YH, He Y, Li MZ, Zheng WY, Ren Y, Li CJ. IL-7 suppresses osteogenic differentiation of periodontal ligament stem cells through inactivation of mitogen-activated protein kinase pathway. *Organogenesis* 2016; **12**: 183-193 [PMID: 27579861 DOI: 10.1080/15476278.2016.1229726]

139   **Kim YG**, Park JW, Lee JM, Suh JY, Lee JK, Chang BS, Um HS, Kim JY, Lee Y. IL-17 inhibits osteoblast differentiation and bone regeneration in rat. *Arch Oral Biol* 2014; **59**: 897-905 [PMID: 24907519 DOI: 10.1016/j.archoralbio.2014.05.009]

140   **Pacios S**, Xiao W, Mattos M, Lim J, Tarapore RS, Alsadun S, Yu B, Wang CY, Graves DT. Osteoblast Lineage Cells Play an Essential Role in Periodontal Bone Loss Through Activation of Nuclear Factor-Kappa B. *Sci Rep* 2015; **5**: 16694 [PMID: 26666569 DOI: 10.1038/srep16694]

141   **Chang J**, Liu F, Lee M, Wu B, Ting K, Zara JN, Soo C, Al Hezaimi K, Zou W, Chen X, Mooney DJ, Wang CY. NF-κB inhibits osteogenic differentiation of mesenchymal stem cells by promoting β-catenin degradation. *Proc Natl Acad Sci U S A* 2013; **110**: 9469-9474 [PMID: 23690607 DOI: 10.1073/pnas.1300532110]

142   **Wang Z**, Jia Y, Du F, Chen M, Dong X, Chen Y, Huang W. IL-17A Inhibits Osteogenic Differentiation of Bone Mesenchymal Stem Cells *via* Wnt Signaling Pathway. *Med Sci Monit* 2017; **23**: 4095-4101 [PMID: 28837545 DOI: 10.12659/msm.903027]

143   **Shaw AT**, Maeda Y, Gravallese EM. IL-17A deficiency promotes periosteal bone formation in a model of inflammatory arthritis. *Arthritis Res Ther* 2016; **18**: 104 [PMID: 27165410 DOI: 10.1186/s13075-016-0998-x]

144   **Chung YS**, Baylink DJ, Srivastava AK, Amaar Y, Tapia B, Kasukawa Y, Mohan S. Effects of secreted frizzled-related protein 3 on osteoblasts in vitro. *J Bone Miner Res* 2004; **19**: 1395-1402 [PMID: 15312239 DOI: 10.1359/JBMR.040412]

145   **Uluçkan Ö**, Jimenez M, Karbach S, Jeschke A, Graña O, Keller J, Busse B, Croxford AL, Finzel S, Koenders M, van den Berg W, Schinke T, Amling M, Waisman A, Schett G, Wagner EF. Chronic skin inflammation leads to bone loss by IL-17-mediated inhibition of Wnt signaling in osteoblasts. *Sci Transl Med* 2016; **8**: 330ra37 [PMID: 27089206 DOI: 10.1126/scitranslmed.aad8996]

146   **Yavropoulou MP**, Xygonakis C, Lolou M, Karadimou F, Yovos JG. The sclerostin story: from human genetics to the development of novel anabolic treatment for osteoporosis. *Hormones (Athens)* 2014; **13**: 323-337 [PMID: 25555179 DOI: 10.14310/horm.2002.1552]

147   **You L**, Chen L, Pan L, Peng Y, Chen J. SOST Gene Inhibits Osteogenesis from Adipose-Derived Mesenchymal Stem Cells by Inducing Th17 Cell Differentiation. *Cell Physiol Biochem* 2018; **48**: 1030-1040 [PMID: 30041240 DOI: 10.1159/000491971]

148   **Theofilopoulos AN**, Dixon FJ. Murine models of systemic lupus erythematosus. *Adv Immunol* 1985; **37**: 269-390 [PMID: 3890479 DOI: 10.1016/s0065-2776(08)60342-9]

149   **Ma L**, Aijima R, Hoshino Y, Yamaza H, Tomoda E, Tanaka Y, Sonoda S, Song G, Zhao W, Nonaka K, Shi S, Yamaza T. Transplantation of mesenchymal stem cells ameliorates secondary osteoporosis

through interleukin-17-impaired functions of recipient bone marrow mesenchymal stem cells in MRL/Lpr mice. *Stem Cell Res Ther* 2015; **6**: 104 [PMID: 26012584 DOI: 10.1186/s13287-015-0091-4]

150   **Liu Z**, Huang F, Luo G, Wang Y, Du R, Sun W, Li J, Yuan X, Cao D, Li Y, Liu C, Liang S, Jin X, Ling S, Wang D. miR-214 stimulated by IL-17A regulates bone loss in patients with ankylosing spondylitis. *Rheumatology (Oxford)* 2020; **59**: 1159-1169 [PMID: 31846044 DOI: 10.1093/rheumatology/kez594]

151   **Sun Y**, Kuek V, Liu Y, Tickner J, Yuan Y, Chen L, Zeng Z, Shao M, He W, Xu J. MiR-214 is an important regulator of the musculoskeletal metabolism and disease. *J Cell Physiol* 2018; **234**: 231-245 [PMID: 30076721 DOI: 10.1002/jcp.26856]

152   **Chang J**, Wang Z, Tang E, Fan Z, McCauley L, Franceschi R, Guan K, Krebsbach PH, Wang CY. Inhibition of osteoblastic bone formation by nuclear factor-kappaB. *Nat Med* 2009; **15**: 682-689 [PMID: 19448637 DOI: 10.1038/nm.1954]

153   **Driessler F**, Venstrom K, Sabat R, Asadullah K, Schottelius AJ. Molecular mechanisms of interleukin-10-mediated inhibition of NF-kappaB activity: a role for p50. *Clin Exp Immunol* 2004; **135**: 64-73 [PMID: 14678266 DOI: 10.1111/j.1365-2249.2004.02342.x]

154   **Németh K**, Leelahavanichkul A, Yuen PS, Mayer B, Parmelee A, Doi K, Robey PG, Leelahavanichkul K, Koller BH, Brown JM, Hu X, Jelinek I, Star RA, Mezey E. Bone marrow stromal cells attenuate sepsis *via* prostaglandin E(2)-dependent reprogramming of host macrophages to increase their interleukin-10 production. *Nat Med* 2009; **15**: 42-49 [PMID: 19098906 DOI: 10.1038/nm.1905]

155   **Chen E**, Liu G, Zhou X, Zhang W, Wang C, Hu D, Xue D, Pan Z. Concentration-dependent, dual roles of IL-10 in the osteogenesis of human BMSCs *via* P38/MAPK and NF-κB signaling pathways. *FASEB J* 2018; **32**: 4917-4929 [PMID: 29630408 DOI: 10.1096/fj.201701256RRR]