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The Key Role of Interleukin-17A/Interleukin-17RA in Bone Metabolism and Diseases: A Review

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ABSTRACT

Bone metabolism requires a balance mechanism between intricate processes of bone formation and resorption, which is affected by the essential interaction between osteoblasts and osteoclasts. Interleukin-17 (IL-17) is a family of cytokines consisting of six isoforms: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F. Among these isoforms, IL-17A has shown promising and novel roles in the regulation of bone metabolism. IL-17A has also captivated the interest of many researchers since its discovery because of its role as a pro-inflammatory cytokine which mediates a few inflammatory processes. This review describes the biology of IL-17A and its receptor as well as summarises the regulatory role of IL-17A in bone metabolism and diseases through some known pathways. Understanding the function of IL-17A in bone metabolism may lead to the development of therapeutics or diagnostic strategies for some bone diseases; as well as future therapy using tissue engineering and regenerative medicine approaches.

Keywords: *Bone disease; bone metabolism; inflammatory cytokine; interleukin-17A; interleukin-17A receptor*

INTRODUCTION

An interesting discovery of which the naive cluster of differentiation (CD4+) T cells can differentiate not only into T helper type 1 (Th1) and T helper type 2 (Th2) subsets but also into the third lineage of Th called T helper type 17 (Th17), had resulted in the discovery of interleukin-17 (IL-17) cytokine, a cytokine with a broad receptor distribution. IL-17 is a group of cytokines that consisting of six isoforms namely IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F. IL-17A or also known as IL-17, being the first member to be discovered, has garnered significant attention, and remains the most extensively studied cytokine within the IL-17 family. The interleukin-17 receptor (IL-17R) is ubiquitously expressed in a wide range of tissues, and the binding of IL-17A/IL-17RA therein exerts specific biological responses, indicating the importance of this interaction in tissue homeostasis as well as in bone diseases. It is a pro-inflammatory cytokine and has vital roles in the development of diseases, especially in the pathogenesis of inflammatory diseases. The importance of these cytokines in promoting the production of other pro-inflammatory molecules such

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as interleukin-6 (IL-6), interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α), chemokine (C-X-C motif) ligand 1 (CXCL1) and chemokine (C-X-C motif) ligand 8 (CXCL8) (Bellini *et al.*, 2012; Meng *et al.*, 2012) contributes to excessive inflammatory responses resulting into chronic inflammation and tissue damage.

The role of IL-17A in the mechanism of osteoclastogenesis is through the regulator gene known as receptor activator of nuclear factor kappa-B ligand (RANKL) (Sato *et al.*, 2006) and also in the mechanism of osteogenesis (Sebastian *et al.*, 2018), suggesting that IL-17A plays a crucial part in bone homeostasis. The process of bone homeostasis is also regulated by several signalling pathways such as the RANK/RANKL/osteoprotegerin (OPG) pathway, mitogen-activated protein kinase (MAPK) signalling pathway, and janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) pathway and studies have shown some key roles of IL-17A in activating regulator genes and protein kinases which are involved in the signalling pathways (Tokuda *et al.*, 2004; Osta *et al.*, 2014; Jo *et al.*, 2018; Sebastian *et al.*, 2018). The fact that IL-17A has an important role in the regulation of bone metabolism has made the cytokine a promising therapeutic target in some bone diseases such as rheumatoid arthritis (RA), ankylosing spondyloarthritis (AS), and psoriatic arthritis (PsA) (Koenders *et al.*, 2005; Jandus *et al.*, 2008; Mei *et al.*, 2011; Menon *et al.*, 2014; Baeten *et al.*, 2015). This review will discuss in detail the biology of IL-17A, its role in pro-inflammatory functions, and its involvement in bone biology and bone diseases.

IL-17A Origin, Family and Receptors

Activated naive $CD4^+$ T cells could differentiate into different functional subsets. The earliest recognised effectors T cell subsets are Th1 and Th2 subsets. The third lineage of Th was identified as Th17 (Dong, 2011). The development and function of this novel T cell subset had become the centre of attention to many researchers. Th17 produces IL-17, IL-17F and IL-22. The development of Th17 cells involves a combination reaction of some differentiation factors such as transforming growth factor beta (TGF-β), IL-6 or IL-21, growth and stabilisation factor which is IL-23, and also the transcription factor such as signal transducer and activator of transcription 3 (STAT3), and transcription factors of the RAR-related orphan nuclear receptor (RORγt and RORα) (Korn *et al.*, 2009). Human IL-17 gene product codes for a protein of 155 amino acids, is secreted by activated CD4+ memory T cells as a homodimer of 30–35 kDa glycoprotein (Fossiez *et al.*, 1996). As a cytokine with broad distribution receptors, the activity and responses may play an important role in tissue homeostasis as well as diseases progression. IL-17 has six members in the cytokine family: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F. Among the members, IL-17A is the most studied member of IL-17 cytokine family. IL-17A was first cloned from murine lymphoid cells and homologous to protein which was enhanced by open reading frame 13 (ORF13) gene in T Lymphotropic Herpesvirus Saimiri (Rouvier *et al.*, 1993). In contrast to IL-17A and IL-17F which are primarily produced in activated T cells; IL-17B, 1L-17C, IL-17D, and IL-17E can be found in a wide variety of tissues. IL-17B mRNA transcript was found to be expressed in a wide range of human adult tissues such as pancreas, small intestine, and stomach whereas IL-17C was constricted only as a rarely expressed sequence tag (EST) found in adult prostate and foetal kidney libraries (Li *et al.*, 2000). IL-17C was rapidly expressed on epithelial cells in response to bacterial and inflammatory stimuli and binds to the receptor complex of IL-17RA and IL-17RE which are favourably expressed on epithelial (Ramirez-Carrozzi *et al.*, 2011). Another IL-17 family member, termed IL-17D was cloned using the rapid amplification of complementary DNA (cDNA) ends (RACE) polymerase chain reaction and exhibits similarities to other

members of IL-17 family in which they have the ability to stimulate the production of cytokines to indirectly modulate the immune response (Starnes *et al.*, 2015). According to the study, IL-17D is highly expressed in a wide range of human tissues such as skeletal muscle, brain, adipose, heart, lung and pancreas. Additionally, IL-17E-producing cells includes those of dendritic cells, macrophages, T cells, eosinophils, basophils, mast cells, epithelial, and paneth cells (Song & Qian, 2013). IL-17E, also known as IL-25, is produced by Th2 cells and mediated Th2 cell responses by inducing the interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13) which caused an increased in immunoglobulin E (IgE) production and eosinophilia (Iwakura *et al.*, 2011). IL-17E was also reported to have a noticeable role in the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-Kb) and stimulated the production of pro-inflammatory chemokine, IL-8 in TK-10 cancer cell line which was derived from the human kidney renal cell adenocarcinoma (Lee *et al.*, 2001). IL-17E (IL-25) requires a receptor complex of two distinct receptors such as IL-17RB and IL-17RA to mediate the IL-25 biological activities (Rickel *et al.*, 2021).

Cytokines regularly deploy their biological functions through their binding to the specific cell surface receptors which sequentially activate signal transduction within the cells. In 1995, a ground-breaking study revealed the discovery of a novel receptor isolated from the Herpesvirus Samiri gene 13, which was found to bind to a previously unknown cytokine. This cytokine was subsequently named IL-17, while its receptor was designated as IL-17R (Yao *et al.*, 1995). Several studies had proven the existence of IL-17RA and the significance of its binding to the cytokines when they introduced monoclonal antibodies against the receptor (IL-17R) which eventually blocked IL-17-mediated function, suggesting the binding is necessary to generate IL-17 specific biological responses (Yao *et al.*, 1997; Zhu & Qian, 2012). Until now, five members of IL-17 receptors had been identified (IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE) which share sequence homology like their ligands. IL-17RA is known to be ubiquitously expressed in wide ranges of tissues and cells type. Several clinical trials had been conducted to evaluate the therapeutic effects of IL-17A by blocking its receptor, the IL-17RA, thus inhibiting IL-17/IL-17R signalling in certain inflammatory autoimmune diseases (Zhu & Qian, 2012). The discovery of IL-17RA and its high affinity binding to IL-17A in humans gives a reaction of cytokine receptor complex which resulted in some important biological functions of IL-17A. Thus, this will help in understanding the functions of IL-17A and acknowledging them in clinical therapy.

Role of IL-17A in Inflammation

Numerous kinds of research have been carried out to identify various roles of IL-17A in inflammation, as evidenced by its important involvement in inflammation. The fact that IL-17A promotes the synthesis of pro-inflammatory chemokines/molecules in pathological conditions strongly suggests that it is a pro-inflammatory cytokine (Song & Qian, 2013). The pro-inflammatory responses result in an excessive inflammation and tissue damage usually in the development of inflammatory diseases.

The pathogenesis of diseases such as liver fibrosis has been linked to IL-17A signalling (Meng *et al.*, 2012) (Fig. 1). In liver fibrosis, IL-17A enhanced the Kupffer cells to release inflammatory cytokines such as IL-6, IL-1, and TNF-α and induced hepatic stellate cells to express collagen, indicating that it has profibrogenic effects (Meng *et al.*, 2012). Fibrocytes activated by IL-17A proliferate and generate pro-inflammatory cytokines CXCL1 and CXCL8, which are hypothesised to enhance the neutrophil recruitment and induce airway hyperresponsiveness (Bellini *et al.*, 2012). Meanwhile, studies involving inflammatory bowel disease found a significant positive association between IL-17A and nitric oxide levels, with a higher

correlation in active Crohn's disease than active ulcerative colitis (Rafa *et al.*, 2013). Subsequent effect in inflammatory bowel disease was also demonstrated which resulted from the synergistic effects of IL-17A, IL-22, and TNF-α (Stallhofer *et al.*, 2018). Co-stimulation of IL-17A was shown to significantly induce cofactor IKBZ mRNA expression which helps TNF-α to induce lipocalin-2 (LCN2), an inflammatory bowel disease marker activity. Thus, the combination of IL-17A, TNF-α, and IL-22 are responsible for the increase of LCN2 expression (Stallhofer *et al.*, 2018). Besides in liver fibrosis and bowel diseases, the function of IL-17A as a pro-inflammatory cytokine also stands out through an airway inflammation which also could be closely related to bone condition.

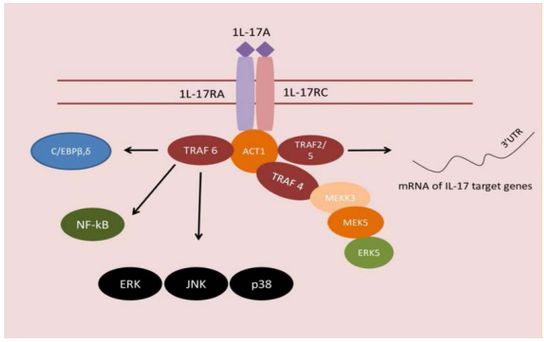

Fig. 1 IL-17A signalling. IL-17 signalling starts through IL-17RA and IL-17RC complex. The receptors recruit Act1, an adaptor molecule for downstream signalling, operating through different TRAF proteins. TRAF6 activation triggers the NF-kB, C/EBPβ, C/EBPδ, and MAPK pathway, which includes extracellular signal-regulated kinase (ERK), p38, and Jun N-terminal kinase (JNK). TRAF4 mediates the activation of ERK5 via the association of IL-17R-Act1 complex with MEKK3 and MEK5. Act1-TRAF2-TRAF5 complex controls mRNA stability of IL-17 target genes (Amatya *et al.*, 2017).

In a study by Xiong *et al.* (2020), it was observed that there is an association between cigarette smoke-induced bone loss and interleukin-17A (IL-17A). The researchers investigated the impact of IL-17A deficiency on cigarette smoke-induced lung inflammation and bone loss in mice. They found that IL-17A-deficient mice exposed to cigarette smoke exhibited partial improvement in total lung capacity and reduced infiltration of inflammatory cells in lung tissues. This was supported by decreased levels of pro-inflammatory cytokines such as IL-6 and IL-1β. Additionally, the IL-17A-deficient mice showed improved trabecular and cortical bone condition, bone mineral density, and bone volume compared to mice exposed to cigarette smoke. Interestingly, another study proved the involvement of IL-17A in autoimmune inflammatory diseases of central nervous system. They used the model of IL-17A-deficient mice and anti-IL-17A treatment during the induction phase which resulted in resistance to autoimmune encephalomyelitis (EAE) induction and delayed clinical signs of the disease (McGinley *et al.*, 2020). Furthermore, IL-17A was shown to be involved in a positive feedback loop that recruited IL-1-secreting myeloid cells, which are responsible for activating pathogenic T cells and Th17 cells. All the studies had demonstrated the dual role of IL-17A as a pro-inflammatory cytokine as well as an anti-inflammatory cytokine. However, further investigations are needed to explore the biological functions of IL-17A as both pro- and anti-inflammatory in diseases to approach for therapeutic strategy.

Role of IL-17A in Bone Metabolism

Bone metabolism entails complex mechanisms of bone growth and resorption that are regulated by the vital relationship between osteoblasts and osteoclasts, as well as hormonal and regulatory factors. Bone metabolism involves several mechanisms and pathways including the RANK/RANKL/OPG pathway, MAPK signalling pathway, and JAK2/STAT3 pathway (Tokuda *et al.*, 2004; Boyce & Xing, 2008; Huang *et al.*, 2009; Kocić *et al.*, 2012; Gu *et al.*, 2013; Walsh & Choi, 2014; Osta *et al.*, 2014; Đorđević *et al.*, 2016; Sritharan *et al.*, 2016; Jo *et al.*, 2018; Sebastian *et al.*, 2018). IL-17A was shown to be significantly greater in the synovial fluid of rheumatoid arthritis patients, and has since become a

key cytokine for osteoclastic bone resorption dependent on osteoblast processes (Kotake *et al.*, 1999). Although IL-17A is thought to be responsible for osteoclastogenesis, it has no direct effects on osteoclast precursor cells. Instead, it promotes osteoclastogenesis by activating RANKL, an apoptosis regulator gene on osteoblast cells (Sato *et al.*, 2006). Subsequent studies had looked into the effects of IL-17A on osteoblasts, and it was discovered that IL-17A stimulated the osteogenic differentiation (Osta *et al.*, 2014; Croes *et al.*, 2016; Sebastian *et al.*, 2018). The stimulation of osteogenic differentiation was evidenced by the increased matrix mineralisation, alkaline phosphatase activity (ALP), and the expression of bone markers such as alkaline phosphatase (ALP), osteopontin (OPN), osteocalcin (OCN), and osteoprotegerin (OPG) after treatment with IL-17A (Sebastian *et al.*, 2018). In addition, IL-17A was also reported to enhance mineralisation activity by increasing calcium deposition following the treatment with the cytokine (Osta *et al.*, 2014; Sebastian *et al.*, 2018; Khalmuratova *et al.*, 2019).

IL-17A can induce osteogenesis through synergistic interactions with TNF-α or bone-morphogenetic protein 2 (BMP-2), respectively (Osta *et al.*, 2014; Croes *et al.*, 2018). IL-17A also exhibited proliferative effects, as demonstrated by a high percentage of cell viability in IL-17A-treated stem cells from human exfoliated deciduous teeth (SHED) during a five-day time in a dose-dependent manner. IL-17A also plays a role in osteogenic differentiation and bone production (Kim *et al.*, 2020). The administration of IL-17A in cultured mouse calvarial cells promoted osteoblast development, as evidenced by an increase in the number of ALP-stained cells after four and seven days of incubation with osteogenic media, as well as an increase in mineralisation at day 21. These pro-osteogenic effects of IL-17A were mediated by reactive oxygen species, which were dependent on the Act1 adaptor protein of IL-17RA (ROX) (Kim *et al.*, 2020). A study demonstrated a significant increase in RUNX2 and BMP2 expressions, as well as matrix mineralisation in human periosteum-derived cells (hPDC) after treatment with IL-17A (Shah *et al.*, 2020). Furthermore, the study investigated on the dual neutralisation of IL-17A and IL-17F with bimekizumab, a monoclonal antibody (anti-IL-17AF) and a type of medication that is used to treat plaque psoriasis. Interestingly, the neutralisation resulted in a significant suppression in osteogenic markers and matrix mineralisation when compared to blocking IL-17A and IL-17F separately.

There are a few signalling pathways that have been linked to the process of bone homeostasis. RANK/RANKL/OPG, MAPK, JAK2/STAT3, BMP, and Wnt/β-catenin are some of the signalling pathways that have been implicated in the bone homeostasis process (Kocić *et al.*, 2012; Wang Z *et al.*, 2017; Jo *et al.*, 2018; Sebastian *et al.*, 2018). Among the signalling pathways, the RANK/RANKL/OPG signalling pathway is the one that has received the most attention (Fig. 2). The RANK/RANKL/OPG is an essential cellular signalling pathway for bone remodelling. Receptor activator of NF-κB (RANK) is a homotrimeric transmembrane protein of TNF receptor superfamily while the receptor activator of NF-κB ligand (RANKL) is a membrane-bound on osteoblasts or secreted by activated T cells. Additionally, osteoprotegerin (OPG) can function as a soluble decoy receptor for RANKL which is secreted by many cell types including osteoblasts (Boyce & Xing, 2008). RANK is a signalling receptor for RANKL and the binding between those two will induce osteoclast differentiation, whereas OPG as a soluble decoy receptor for RANKL will act as a negative regulator of RANK signalling, thus inhibiting osteoclastogenesis (Walsh & Choi, 2014). Previously, treatment with IL-17A and TNF-α alone had significantly reduced the RANKL mRNA level and combination of these two had resulted in a more profound decrease of RANKL mRNA level, thus promoting osteogenesis (Osta *et al.*, 2014). It was also demonstrated that

the combination treatment of IL-6 and IL-17A had improved the OPG/RANKL ratio, hence promoting osteogenesis and diminished osteoclastogenesis in murine osteoblast cells (Sritharan *et al.*, 2016). Later study also demonstrated that IL-17A induced proliferation and promoted osteogenic differentiation in stem cells from human exfoliated deciduous teeth (SHED) by altering the OPG/RANKL ratio (Sebastian *et al.*, 2018). These findings shed light on the role of IL-17A in the RANK/RANKL/OPG signalling pathway, which regulates the bone homeostasis.

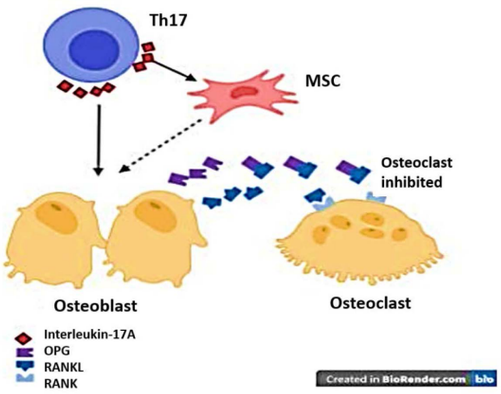

Fig. 2 RANK/RANKL/OPG signalling pathway. IL-17 has a role in the regulation of bone homeostasis process through RANK/RANKL/OPG signalling pathway. Th17 cells produce IL-17 which stimulates the production of RANKL in osteoblasts and accelerates osteogenic differentiation of mesenchymal stem cells. RANKL binds to its receptor RANK, which is located on osteoblast membranes. The bindings are crucial for osteoclast differentiation. Meanwhile, OPG, a soluble decoy receptor produced by osteoblasts will inhibit the osteoclast differentiation via its binding to RANKL.

MAPK signalling pathway is another important regulator in bone metabolism and is a type of protein kinase that phosphorylates its own amino acids serine and threonine. MAPK regulates some important cell functions including proliferation, gene regulation, differentiation, cell survival as well as apoptosis in response to various stimuli. There are three common MAPK pathways established in the mammalian cells classified according to their activation motif, structure, and function. They are grouped as extracellular signal-regulated kinase 1/2 (ERK1/2), Jun N-terminal kinase (JNK) and p38. According to some studies, IL-17 stimulation substantially stimulates MAPK signalling by increasing the phosphorylation of protein kinases (Tokuda *et al.*, 2004; Huang *et al.*, 2009; Kocić *et al.*, 2012). The involvement of IL-17A in bone metabolism through MAPK signalling pathway specifically p38 MAPK was reported previously (Tokuda *et al.*, 2004). Stimulation of IL-17 on the human bone marrow-derived mesenchymal stem cells had resulted in the increased phosphorylation of MEK-ERK pathway in the presence of ROS generation (Huang *et al.*, 2009). Similar findings found that IL-17 activated the MAPK signalling pathway by increasing the phosphorylation of both ERK1/2 and p38 in their investigation (Kocić *et al.*, 2012). In contrast, IL-17 had also been reported to inhibit both proliferation and migration of periodontal ligament stem cells (PDLSC) and significantly decreased their osteogenic differentiation through the activation of ERK1/2 and JNK pathways (Đorđević *et al.*, 2016).

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway are required for skeletal development, namely in the osteoblast and osteoclast biology (Galipeau, 2013). IL-17A regulates osteoblast activity by promoting ALP activity and mineralisation activity via activation of JAK2/STAT3 signalling pathway in ankylosing spondylitis (Jo *et al.*, 2018). Another signalling pathway, Wnt signalling was first reported to have been linked to skeletal development, when Wnt3a-deficient embryos were discovered to have axial defects (Takada *et al.*, 1994). The loss of β-catenin in mature osteoblasts and/or osteocytes causes severe osteopenia and enhanced osteoclastogenesis (Glass *et al.*, 2005; Holmen *et al.*, 2005). In contrast, treatment with IL-17A had inhibited the osteogenic differentiation of bone mesenchymal stem cells (BMSCs) and

up-regulated the expression of Wnt signalling pathway inhibitor (sFRP1) while down-regulating the expression of Wnt3 and Wnt6 (Wang Z *et al.*, 2017).

There are not many studies discussing the effect of IL-17A on the BMP signalling pathway. However, the interaction between IL-17 as pro-inflammatory cytokines and BMP signalling pathway has been addressed. A study stated on the activation of BMP signalling pathway in rheumatoid arthritis (RA) by showing an increase in the expressions of certain BMP receptors type, BMP ligands, and BMP target genes in RA synoviocytes. They also demonstrated the interaction between important pro-inflammatory cytokines involved in RA such as TNF-α and IL-17A and the expression of certain components in BMP signalling pathway (Varas *et al.*, 2015). Blocking signalling produced by BMP ligands enhanced the expression of IL-8 and granulocyte macrophage-colony stimulating factor indicating that BMP ligands blocked the TNF-α/IL-17-induced cytokines. This shows that BMP ligands produced via autocrine pathway interfere with the effects of pro-inflammatory cytokines presence in RA joints (Varas *et al.*, 2015). Although IL-17A has become a responsible cytokine for osteoclastogenesis in certain autoimmune diseases, no study shows its direct effect on the osteoclast cells themselves. In fact, IL-17A was actively investigated for its pro-osteogenic effects and how the cytokine could play important role in bone homeostasis which can be explored through different signalling pathways.

Role of IL-17A in Bone Diseases

IL-17A has been implicated in both metabolic and inflammatory bone diseases. Bone metabolic diseases such as osteoporosis and inflammatory bone diseases such as rheumatoid arthritis are among the diseases that have been reported to be regulated by IL-17A. Osteoporosis is a metabolic bone disease characterised by a reduction in skeletal mass due to an imbalance in bone resorption and formation processes. Several studies reported the association between osteoporosis and the level of IL-17A. There was an increase in the number of Th17 cells and circulating IL-17A levels in the ovariectomised mice which induced the RANKL activity and promoted bone loss in the estrogen-deficient mice (Tyagi *et al.*, 2012; DeSelm *et al.*, 2013). A study showed the increased level of Th17 cells and IL-17A were associated with low bone mineral density in postmenopausal women (Bhadricha *et al.*, 2021). While some studies reported IL-17A to be a mediator of ovariectomised-induced osteoporosis, others found IL-17 receptor signalling to be bone-protective. Scheffler *et al.* (2020) explained the differences by demonstrating for the first time that IL-17A depletion had differential effects on ovariectomised-induced osteoporosis, with IL-17A being essential for cortical but not trabecular bone loss.

Numerous researchers concurred on the pro-inflammatory roles of IL-17A and its involvement in the inflammatory bone diseases, indicating its pathological roles in the diseases. One of the first diseases to be linked to IL-17A was rheumatoid arthritis (RA), a chronic inflammatory disease primarily affecting the joints. The effect of IL-17A in increasing bone loss in rheumatoid arthritis mouse models has been studied extensively. A study by Lubberts *et al.* (2004) had described the effect of neutralising anti-IL-17 antibody in collagen-induced arthritis (CIA) model which significantly reduced systemic IL-6 levels as well as synovial IL-1-positive and RANKL-positive cells; which had resulted in a significant reduction in the severity of the disease, including joint damage suppression and cartilage and bone destruction prevention. Further investigation in experimental arthritis model demonstrated the down-regulation of IL-1β, TNF-α, and RANKL levels, as well as preventing bone erosion and joint inflammation following IL-17 neutralisation, indicating the crucial role of IL-17A in RA (Koenders *et al.*, 2005). These results showed that IL-17A plays a major role in pathologically

promoting rheumatoid arthritis, owing to the downregulation of IL-17A-induced pro-inflammatory mediators (IL-1 and TNF-α) and a modulation in the RANKL/OPG ratio. The important involvement of IL-17A in RA was evidenced by high levels of Th17 cells, IL-17A, and its receptor in synovial fluid of the RA patients (Kohno *et al.*, 2008; Gaffen, 2009; Elhewala *et al.*, 2015; Dhaouadi *et al.*, 2018).

The roles of IL-17A in pathogeneses of axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) have been reported (Mei *et al.*, 2011; Blauvelt & Chiricozzi, 2018). Although IL-17A in ankylosing spondylitis was not directly or strongly correlated to the disease activity as in RA, a study found that serum IL-17A and IL-23 levels in the ankylosing spondylitis patients are elevated compared to healthy patients; which suggested that these cytokines may play critical roles in the pathogenesis of ankylosing spondylitis (Mei *et al.*, 2011). The crucial involvement of IL-17A in the pathogenesis of ankylosing spondylitis may suggest the potential therapeutic target of the disease. In clinical trials of secukinumab (anti-interleukin-17A), ankylosing spondylitis patients who received the treatment showed significant reduction in the signs and symptoms of the disease after 16 weeks of the treatment (Baeten *et al.*, 2015). The validation of this cytokine inhibition as a therapeutic strategy for ankylosing spondylitis is also supported by another clinical trial with ixekizumab (anti-interleukin-17A) in patients. Treatment with ixekizumab resulted in the improvement of signs and symptoms of radiographic ankylosing spondylitis as compared to placebo groups (van der Heijde *et al.*, 2018). IL-17A secretion was shown to be influenced by IL-23; hence similar responses of IL-17A inhibition and IL-23 inhibition were expected in human diseases (Sieper *et al.*, 2019). However, a few trials with IL-23 inhibitors (ustekinumab and risankizumab) reported no improvement in axial spondyloarthritis activity (Baeten *et al.*, 2018; Deodhar *et al.*, 2019). This disengagement event between IL-17A and IL-23 has been described in an intriguing review (Sieper *et al.*, 2019). They hypothesised that the discrepancy could be attributable to the unique immunopathological milieu that axial spondyloarthritis creates. This could be explained by the fact that IL-17A secretion occurred in the absence of IL-23. Furthermore, there have been debates on the source or primary cell types that produce IL-17A in the pathogenesis of axial spondyloarthritis, which is still unclear (Sieper *et al.*, 2019).

Psoriatic arthritis is a chronic, immune-mediated, inflammatory skin disease that is driven by pro-inflammatory cytokines characterised by altered keratinocytes differentiation and also affected the joint and bone (Gottlieb *et al.*, 2005). Few reviews have been published to critically discuss on the involvement of IL-17A in the pathogenesis of psoriatic arthritis (PsA) as well as IL-17/1L-17R targeted therapeutics (Lubrano & Perrotta, 2016; Wang EA *et al.*, 2017; Blauvelt & Chiricozzi, 2018). It was reported that synergistic effects of IL-17A with TNF-α had up-regulated the keratinocyte genes expression in psoriatic skin (Chiricozzi *et al.*, 2011).

Another study has been conducted to demonstrate the involvement of Th17 in psoriatic arthritis patients. Jandus *et al.* (2008) had carried out a study to evaluate the frequency and functional properties of Th17 cells in patients with different autoimmune diseases including psoriatic arthritis and ankylosing spondylitis compared to healthy donors. The study reported an increased level of Th17 cells in peripheral blood of patients with psoriatic arthritis and ankylosing spondylitis compared to healthy donors, suggesting the role of Th17 cells in the pathogenesis of the diseases (Jandus *et al.*, 2008). In addition, Menon *et al.* (2014) investigated the possible role of IL-17-producing CD8+ T cells in psoriatic arthritis disease process and suggested IL-17 as the key mediator in synovial inflammation. The study compared the level

of IL-17+CD4+ T cells and IL-17+CD4- T cells in synovial fluid and peripheral blood of patients with psoriatic arthritis and rheumatoid arthritis and found that only the level of IL-17+CD4+ T cells significantly elevated in synovial fluid compared to peripheral blood of rheumatoid arthritis patients. In addition, for the first time they also proved that besides IL-17+CD4+ T cells, IL-17+CD4- T cells, comprised mainly of CD8+ cells were also significantly enhanced in synovial fluid compared to peripheral blood of patients with psoriatic arthritis and the frequency of IL-17+CD4- T cells (predominantly CD8+ cells) were positively associated with C reactive protein level, erythrocyte sedimentation rate, and disease activity score in 28 joints of patient. Thus, they concluded that psoriatic arthritis joint is enriched with IL-17+CD8+ T cells and these cells contribute to the pathogenesis of psoriatic arthritis disease (Menon *et al.*, 2014).

Primary sclerosing cholangitis (PSC) is a cholestatic liver disease characterised by progressive bile duct destruction and can lead to serious complications such as osteoporosis. A study showed 15% out of 237 PSC patients had osteoporosis complications (Angulo *et al.*, 2011). A previous study investigated the mechanism of PSC-related bone loss and discovered that low bone mass in PSC patients was linked to bone resorption (Schmidt *et al.*, 2019). The study also found a link between deoxypyridinoline (Dpd) level, a bone resorption biomarker, and the frequency of Th17 cells, as well as that IL-17AF deficiency and IL-17A neutralisation corrected osteopenia in a mouse model of PSC patients (Abcb4-/-), implying that IL17A produced by Th17 cells is a mediator of PSC-related bone loss. Due to its varying roles in different bone diseases, it is crucial to conduct comprehensive research on each specific bone disease when developing therapeutic strategies. This approach is necessary to gain a deeper understanding of how IL-17A functions in different contexts and to tailor effective treatment approaches accordingly. The roles of IL-17A on bone formation and diseases in in vivo and in vitro studies are tabulated in Tables 1 and 2.

Table 1 The roles of IL-17A on bone formation and diseases in in vivo studies

Animal	Animal model	Methods	Results	References
IL-17A$^{-/-}$ mice C57BL/6 mice	Normal animal model	IL-17A$^{-/-}$ mice were generated. A drill hole injury was made to mimic femoral cortical bone defect. IL-17A and other inflammatory cells were assessed in the drill hole.	Level of IL-17A increase in the cells of repair tissue. The new bone formed in the drill hole of IL-17A$^{-/-}$ mice are much smaller compared to wild-type mice after 14 and 21 days. IL-17A$^{-/-}$ mice has lower ratio of osteoblast to bone surface.	Ono *et al.*, 2016
Balb/c mice	Proteoglycan-induced spondylitis mice (PGISp mice)	Mice were injected intraperitoneal with decorin for 7 months.	Levels of relative mRNA expression of IL17A are significantly high in lumbar with new bone formation of PGISp mice.	He *et al.*, 2017

Table 2 The roles of IL-17A on bone formation and diseases in in vitro studies

Type of samples	Sources	Methods	Results	References
Human mesenchymal stem cells	Bone marrow from healthy donor.	Cells undergo osteogenic differentiated for 21 days in the presence or absence of TNF-α and/or IL-17A.	IL-17A potentiate the effect of TNF-α in osteogenic differentiation through ALP activity, matrix mineralisation and BMP2 expression.	Osta *et al.*, 2014
Bone explants Fibroblast-like-synoviocytes	From tibia/ femoral head. Synovial tissue hips/knees from RA/OA donor.	Treatment of bone explants with TNF-α and/or IL-17A for 7 days. Cells undergo osteogenic differentiated for 17 days in the presence or absence of TNF-α and/or IL-17A.	Combination of TNF-α and IL-17A induced osteogenic differentiation of FLS. RA-FLS has more potent response in ALP activity and production of IL-6/IL-8.	Osta *et al.*, 2015
Fibroblast-like-synoviocytes	Synovial tissue of hips/knees from RA/OA donor.	FLS undergo osteogenic differentiated for 21 days in the presence or absence of TNF-α and/or IL-17A.	IL-17A and/or TNF-α treatment enhance osteogenic differentiation of FLS. RA-FLS are more sensitive to the treatment, reflected to an increase in schnurri-3 expression.	Lavocat *et al.*, 2016
MC3T3-E1cells	Immature osteoblasts from normal mice model.	Treatment of IL-6 and/or IL-17A onto MC3T3-E1 cells.	Treatment of IL-6 and/or IL-17A significantly increase ALP and OPG and decrease RANKL expressions. Combination of IL-6/IL-17A significantly increase OPG/RANKL ratio.	Sritharan *et al.*, 2016
MC3T3-E1cells	Immature osteoblasts from normal mice model.	Induction of hydroxyapatite onto MC3T3-E1 cells with IL-6 and/or IL-17A treatment for 14 days.	Synergistics effect of IL-6/IL-17A promote better adhesion on hydroxyapatite and promote osteoblastic differentiation by improving OPG/RANKL ratio.	Sritharan *et al.*, 2018
Stem cells derived from human exfoliated deciduous teeth (SHED)	Dental pulp tissue (healthy).	SHED undergo osteogenic differentiation with IL-17A treatment for 21 days.	IL-17A treatment enhance osteogenic differentiation by increasing mineralisation and osteogenic markers expressions as well as improving OPG/RANKL ratio.	Sebastian *et al.*, 2018
Mouse calvarial cells	Newborn C57BL/6 mice (normal mice model).	Calvarial cells were cultured in osteogenic media with treatment of IL-17A for 7 and 21 days. Co-cultures between calvarial cells and mouse bone marrow macrophages for 7 days.	IL-17A enhance osteoblast differentiation in dose-dependent manner by increasing ALP-stained cells at day 4 & 7 and a significantly increase in mineralisation occurs at day 21. Co-culture experiment with IL-17A increase TRAP activity and number of osteoclasts.	Kim *et al.*, 2020

(*continued on next page*)

Table 2 (*continued*)

Type of samples	Sources	Methods	Results	References
Peri-entheseal bone (PEB) Peri-entheseal soft tissue (EST)	Human spinous process. Human interspinous ligament.	PEB & EST were expanded into MSCs and cultured in osteogenic media with treatment of IL-17A and/or TNF.	MSCs from PEB has higher capability compared to EST to osteogenically differentiate IL-17A induction increase calcium production in both PEB and EST while TNF induction only enhances osteogenesis in PEB. Combination of IL-17A/TNF enhance osteogenesis in both PEB and EST	Russell *et al.*, 2021
Bone marrow-derived MSC	Balb/c mice (Normal mice model).	BMSCs were induced into MSC1/2, followed by treatment of decorin or low or high level IL-17A to the effect of MSC1 and MSC2 polarisations, respectively. The treatment of anti-IL-17A was also included in IL-17A treated MSCs.	The expressions of TLR4 of MCSs are higher after the treatment of decorin and low level of IL-17A while levels of TLR3 expression are higher after the treatment of high level of IL-17A. Alizarin red staining shows stronger staining after the treatment of high level of IL-17RA .	He *et al.*, 2017

CONCLUSION

IL-17 is an important cytokine that is produced by Th17, a subpopulation of Th cells, has been extensively researched for its role in bone metabolism. On top of that, IL-17A is a founding member of IL-17 cytokine family that are broadly discovered and recognisable among researchers through significant studies. According to earlier investigations, IL-17A has been widely established to have pro-osteoclastogenic effects, particularly in certain inflammatory bone diseases such as rheumatoid arthritis. However, current investigations have also been directed to the role of IL-17A in bone homeostasis. We have summarised some of the critical roles of IL-17A as a key regulator in bone metabolism in this review. However, more research is needed to understand the osteogenic properties of IL-17A on osteogenic differentiation, as well as the molecular and cellular mechanisms that regulate IL-17A in bone metabolism. In addition, limited works have been conducted on the role of IL-17A in disease development as a pro-osteogenesis factor. As a result, future research may be directed to these approaches to establish a substantial role for IL-17A in bone metabolism in both normal and pathological conditions. A better understanding of the physiologic and pathologic roles of IL-17 in bone metabolism will assist in the future development of therapies for bone-related diseases and will contribute to advancements in regenerative strategies for bone tissue engineering.

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