

# The Function and Mechanism of Anti-Inflammatory Factor Metrnl Prevents the Progression of Inflammatory-Mediated Pathological Bone Osteolytic Diseases

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**Abstract:** Metrnl, recently identified as an adipokine, is a secreted protein notably expressed in white adipose tissue, barrier tissues, and activated macrophages. This adipokine plays a pivotal role in counteracting obesity-induced insulin resistance. It enhances adipose tissue functionality by promoting adipocyte differentiation, activating metabolic pathways, and exerting anti-inflammatory effects. Extensive research has identified Metrnl as a key player in modulating inflammatory responses and as an integral regulator of muscle regeneration. These findings position Metrnl as a promising biomarker and potential therapeutic target in treating inflammation-associated pathologies. Despite this, the specific anti-inflammatory mechanisms of Metrnl in immune-mediated osteolysis and arthritis remain elusive, warranting further investigation. In this review, we will briefly elaborate on the role of Metrnl in anti-inflammation function in inflammation-related osteolysis, arthritis, and pathological bone resorption, which could facilitate Metrnl's clinical application as a novel therapeutic strategy to prevent bone loss. While the pathogenesis of elbow stiffness remains elusive, current literature suggests that Metrnl likely exerts a pivotal role in its development.

**Keywords:** osteolysis, bone resorption, bone loss, Metrnl, arthritis, stiff elbow

## Introduction

Imbalance of bone metabolism disrupts the physiological function of osteoblasts, osteocytes and osteomacs. This disruption transforms into a pathological condition characterized by progressive bone resorption. Inflammation plays a significant role in this impairment, particularly in various osteolytic bone diseases, where it predominantly shifts the balance towards bone resorption.<sup>1</sup> A variety of chronic inflammatory bone diseases have been shown to be associated with physiological osteolysis, including rheumatoid arthritis (RA), spondylarthritis, osteoporosis, periodontitis, bone metastasis of malignant tumor, periprosthetic osteolysis due to aseptic loosening.<sup>2,3</sup> Multiple immune-related molecules have been proved to play a crucial role in bone metabolism, such as IL-1 $\beta$ , IL-6, IL-10, IL-17 and TNF- $\alpha$ . These cytokines, serving as primary stimulators of osteoclastogenesis, can upregulate the expression of crucial factors involved in osteoclast differentiation, which is a key driver in the progression of pathological bone resorption.

Metrnl (IL-41, Meteorin-like, Subfatin, Cometin), a secreted protein expressed in white adipose tissue,<sup>4</sup> barrier tissues,<sup>5,6</sup> and activated macrophages,<sup>5</sup> has been confirmed as an adipokine, neurotrophic, and anti-inflammatory cytokine. This factor demonstrates a multitude of physiological functions by activating various intracellular signaling pathways across different cell types including adipocytes, macrophages, myocytes and cardiomyocytes, such as the promotion of neurite outgrowth,<sup>7</sup> improvement of cognitive dysfunction,<sup>8</sup> inflammation inhibition,<sup>5,7</sup> regulation of energy homeostasis,<sup>7,9</sup> and insulin sensitivity,<sup>7,10</sup> enhancement of the browning of white adipose tissue,<sup>7</sup> skeletal muscle regeneration,<sup>11</sup> and heart protection.<sup>12-14</sup> Current research suggests that Metrnl has potential to be biomarker and therapeutic target for diseases associated with inflammation. Nonetheless, the

anti-inflammatory properties and mechanism in immune inflammation-related osteolysis and arthritis remains not fully understood, and further investigation is necessary to elucidate its potential role in these conditions.

Recent studies have highlighted that Metrnl play a regulatory role in bone metabolism and immune inflammation. Multiple studies focused on the correlation of Metrnl and bone arthritis associated with metabolism<sup>15–17</sup> or inflammation, including arthritis<sup>18–21</sup> and osteolysis.<sup>3,22</sup> This review aims to briefly elaborate on the anti-inflammatory function of Metrnl in inflammation-related osteolysis, arthritis, and pathological bone resorption, which could explore the potential of Metrnl as a novel therapeutic strategy in preventing these diseases.

## Metrnl and Immune Inflammation

Metrnl is increasingly recognized as a novel immunoregulatory cytokine intricately linked to inflammatory processes.<sup>5,20</sup> Both the expression of Metrnl and its circulating concentrations show an upsurge in inflamed tissues or in the context of inflammatory diseases. Research has documented that Metrnl is instrumental in modulating inflammatory responses and is closely associated with various inflammation-related disease, including RA, and psoriasis RA,<sup>5</sup> airway inflammation.<sup>23</sup>

Rao et al reported that Metrnl exerted an anti-inflammatory function by increasing the expression of IL-4 and promoting alternative activation of macrophages.<sup>24</sup> Exercise mediates its anti-inflammatory effects by upregulating Metrnl expression in various muscle depots. Additionally, recombinant Metrnl has been shown to suppress the NLRP3 inflammasome, subsequently inhibiting the secretion of IL-1 $\beta$  and IL-18 in BMDMs.<sup>25</sup> This mechanism highlights the potential therapeutic value of Metrnl in modulating inflammation-related pathways. Its levels are significantly elevated in patients with asthma and in mouse models of allergic asthma induced by house dust mite (HDM) extract. Notably, Metrnl plays a critical role in attenuating the pathophysiology of airway hyperreactivity. It reduces inflammatory cell infiltration in the airways and diminishes type 2 cytokine production. This action is associated with the downregulation of dendritic cell (DC)-mediated adaptive immune responses.<sup>23</sup>

A study reported that Metrnl confers protection against LPS-induced acute lung injury (ALI) by activating ferroptosis pathway.<sup>26</sup> In the context of LPS-induced ALI, there is a marked reduction in Metrnl levels accompanied by an upsurge in ferroptosis within the lung tissue. The overexpression of Metrnl mitigated LPS-induced ferroptosis by regulating SIRT1-P53-SLC7A11 signaling and furthermore decrease ALI severity.<sup>26</sup>

Metrnl plays a crucial role in tumour development. Akkus et al observed a histopathological increase in immunoreactivity of Metrnl in IDC samples.<sup>27</sup> The expression of Metrnl has been observed to be significantly upregulated in colorectal cancer tissues as compared to normal tissues, indicating its potential as a prognostic marker.<sup>28</sup> Moreover, the authors observed an association between increased Metrnl expression levels and advanced clinical stage in colorectal cancer patients, suggesting that Metrnl could serve as a predictor for poor prognosis. Kocaman et al reported an increase in Metrnl expression in malignant mesothelioma tissues, suggesting its potential as a diagnostic biomarker for this particular malignancy.<sup>29</sup>

Metrnl was possibly associated with sepsis pathogenic mechanism. Animal study confirmed that in a sepsis model induced by endotoxin, the blood concentrations of Metrnl increased sharply. A deficiency in Metrnl could heighten susceptibility to mortality in mice. Furthermore, Metrnl acts as a co-activator in mitigating inflammation in sepsis-induced renal injury, primarily through the activation of PPAR $\delta$ -dependent pathways.<sup>30</sup> A separate study revealed that serum Metrnl levels in ICU patients with sepsis are inversely correlated with the concentrations of pro-inflammatory cytokines (IL-1 $\beta$ , IL-6, IL-8, IL-17, TNF- $\alpha$  and PCT). Metrnl produced markedly and regulated the differentiation and recruitment of macrophages in sepsis patients, which significantly affected the host defense against sepsis and modulates the balance between Treg/Th17 in the immune response.<sup>31</sup>

Metrnl has been shown to inhibit the secretion of TNF $\alpha$  and MCP-1, and the phosphorylation of NF- $\kappa$ B and I $\kappa$ B in LPS-treated HUVECs and THP-1 cells. This suppression occurs through the enhancement of the phosphorylation of AMPK and the expression of PPAR $\delta$ .<sup>32</sup> Additionally, Metrnl mitigated myocardial ischemia/reperfusion (MI/R)-induced apoptosis in cardiomyocytes by alleviating endoplasmic reticulum stress. This protective effect is mediated via the activation of the AMPK-PAK2 signaling pathway in H9C2 cells.<sup>33</sup>

Studies have identified significant correlations between serum Metrnl levels and the presence and severity of type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD). In patients with T2DM or CAD, serum Metrnl

levels demonstrated a negative correlation with pro-inflammatory markers (high-sensitivity C-reactive protein and IL-1 $\beta$ ), but a positive correlation with the anti-inflammatory cytokine (IL-11).<sup>34,35</sup> Liu et al reported that exercise can increase the production of Metrnl in skeletal muscle of CAD patients by suppressing the glucose metabolic dysfunction of HUVEC and reducing the expression of NLRP3 inflammasome, and subsequently improve patient atherosclerosis.<sup>36</sup>

Ushach et al<sup>5</sup> verified that Metrnl is derived primarily from macrophages and barrier tissues and is involved in the functions associated with macrophages, including anti-inflammatory response, wound healing and tissue remodeling. Metrnl production in macrophages is regulated by a complex interplay of multiple cytokines, such as TNF- $\alpha$ , IL-4, IL-12, IL-17 $\alpha$  and IL-1 $\beta$ , and conversely, Metrnl influences the production of other cytokines and chemokines, such as IL-6, IL-10, CCL2, CXCL1.<sup>5,37</sup> The study also verified that the expression of Metrnl in macrophages is strongly induced by LPS, and its levels parallel the development and resolution of inflammatory responses *in vivo*, which suggested that Metrnl is a new major player in inflammatory responses and is likely to play a crucial role in the pathogenesis of human inflammatory diseases. Notably, Metrnl expression in macrophages is robustly induced by LPS, and its levels are closely aligned with the progression of inflammatory responses *in vivo*, which suggested that Metrnl is a significant contributor to inflammatory responses and the pathogenesis of various human inflammatory diseases.<sup>37</sup>

## Metrnl, Inflammation and Bone Diseases

Multiple studies have identified that Metrnl is involved in bone development, remodeling, and various bone-related pathologies. Gong et al reported that Metrnl may influence osteoblast differentiation and thus bone development.<sup>17</sup> Further research has demonstrated that Metrnl can enhance osteoblast differentiation and mineralization *in vitro*, as well as facilitate bone fracture healing.<sup>15</sup> Additional studies have observed abnormal expression of Metrnl in the cartilage tissue and synovium associated with skeletal diseases.<sup>19</sup> Metrnl in different tissues might have different mechanisms. In patients with OA, the levels of Metrnl in serum were significantly lower than in normal healthy controls, but higher in synovial fluid.<sup>19</sup> These findings underscored the important role of Metrnl in bone diseases. However, the precise mechanism of action of Metrnl in these contexts remains to be elucidated through further research.

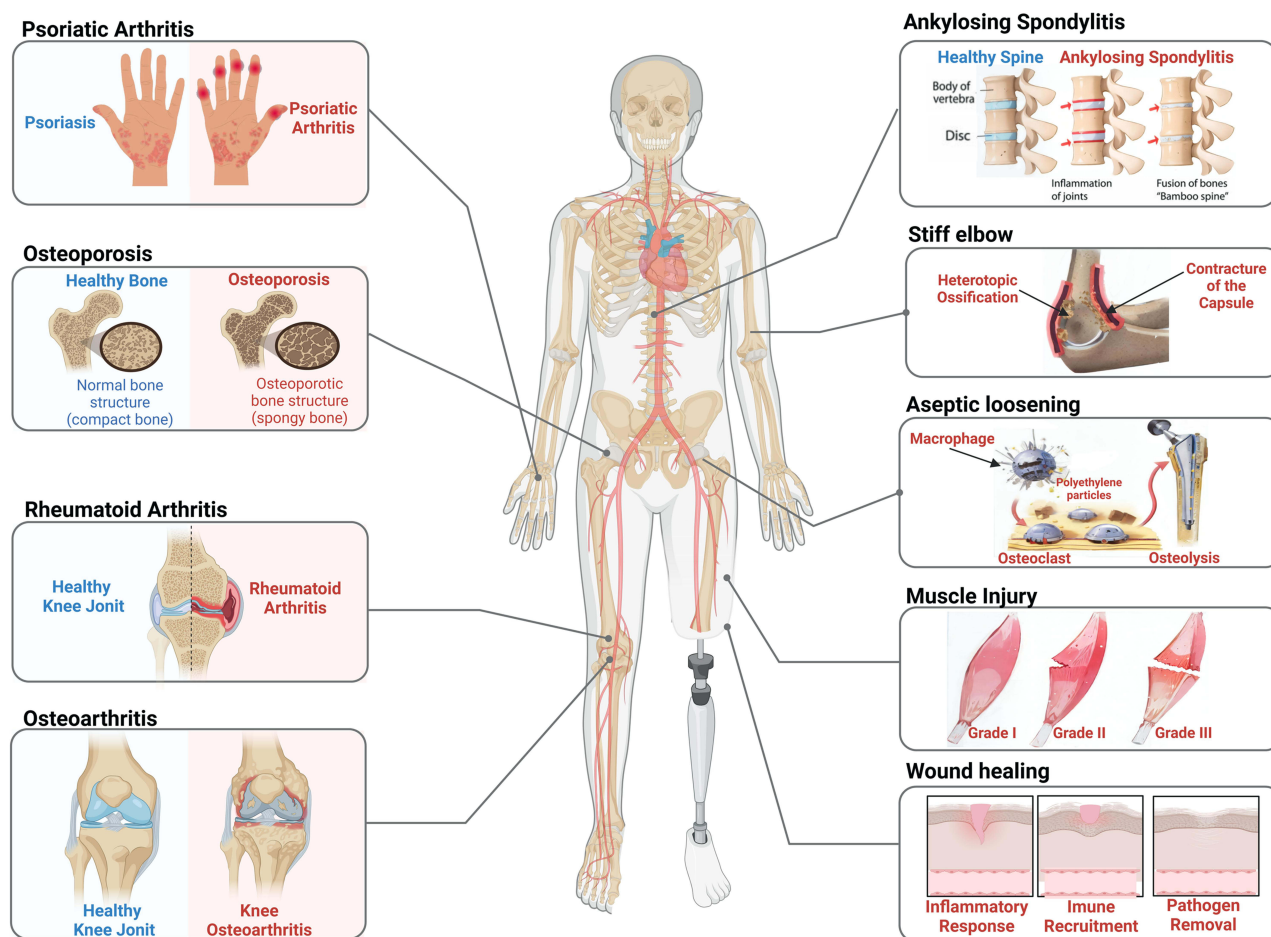
Chronic inflammation is beneficial to a catabolism, promoting osteolysis and reducing both bone formation and bone mineral density.<sup>38,39</sup> Immune inflammation and overexpression of pro-inflammatory cytokines (IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ) are associated with bone health issues, which have destructive impact on normal bone homeostasis through various mechanisms.<sup>40</sup> Catabolic states associated with immune inflammation and pathological bone loss are exemplified in a range of skeletal disorders, including periprosthetic osteolysis,<sup>3,41</sup> aseptic loosening,<sup>42,43</sup> osteoporosis, and rheumatoid arthritis. These conditions are major contributors to disability and impose a significant financial burden globally (Figure 1). Their complex etiology and substantial impact highlight the urgency for effective therapeutic strategies and a deeper understanding of their underlying mechanisms.<sup>44-46</sup>

## Metrnl and Psoriatic Arthritis

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy intricately linked to psoriasis and part of the broader Spondyloarthritis (SpA) spectrum. PsA is characterized by its ability to affect spine, peripheral joints, and entheses, presenting with distinctive clinical features, such as sacroiliitis, enthesitis, dactylitis, spinal involvement, and concurrent psoriasis. Radiologically, PsA can manifest with erosive lesions or osteolysis, as well as periarticular new bone formation, reflecting its diverse impact on bone structure.<sup>47,48</sup> PsA is associated with inflammatory lesions at the entheses, the site where tendons and ligaments attach to the bone. Notably, Metrnl expression is significantly elevated in both the synovial fluid and synovial tissue of PsA patients compared to those with OA. Furthermore, entheses stromal cells have been identified as the primary source of Metrnl production in PsA. This differential expression underscores the distinct pathophysiological mechanisms underlying PsA and suggests a potential role for Metrnl in its diagnosis or treatment.<sup>20</sup> The important role of Metrnl in PsA immunopathogenesis needs further research.

## Metrnl and Osteoporosis

Osteoporosis, predominantly an age-related pathology, is defined as a bone disease characterized by reduced bone mineral mass and microarchitectural degradation of bone tissue. This leads to a decrease in bone strength and



**Figure 1** The functions of *Metn1* in inflammatory-mediated pathological bone osteolytic diseases. Created with BioRender.com. *Metn1* is correlated with some metabolic and inflammatory orthopedic diseases. Studies indicated it play crucial roles in inflammatory reactions, bone metabolism, osteogenesis, muscle regeneration and angiogenesis, and have deep relationship with the development of multiple orthopedic diseases, like psoriatic arthritis, osteoporosis, rheumatoid arthritis, osteoarthritis, axial spondyloarthritis, aseptic loosening, elbow stiffness, muscle injury and wound healing.

significantly increases the risk of osteoporotic fractures, especially in the elderly population worldwide. Conversely, sarcopenia is characterized by progressive muscle wasting, which heightens the risk of injuries, predominantly due to falls. The concurrent development of these conditions underscores the complexity of age-related musculoskeletal decline. Osteoporosis is currently attributed to various endocrine, age, metabolic and mechanical factors. Various evidences suggest that inflammation and muscle–bone crosstalk also exert significant influence on bone metabolism, leading to bone loss. An imbalance in bone mesenchymal stem cells favoring adipogenesis over osteogenesis is detrimental to bone health, often resulting in a decrease of bone mass and the development of osteoporosis.<sup>49</sup> Muscle and bone exhibit a closely interlinked development and growth process. Consequently, muscle disuse or atrophy often precipitates osteoporosis, highlighting the intrinsic connection between these two tissues.<sup>50</sup> Muscle–bone crosstalk, encompassing both biomechanical and biochemical interactions, plays a crucial role in bone remodeling.<sup>51</sup> *Metn1* as an immune/metabolic regulator, plays a pivotal role in modulating the activity of diverse cell types, and in both innate and acquired immune responses. It exhibits a distinctive expression pattern primarily observed in hypertrophic chondrocytes and osteoblasts.<sup>52</sup> Moreover, its overexpression has been shown to effectively impede mineralized nodule formation and hinder osteoblast differentiation.<sup>17</sup> It has been proved in whole-body or macrophage-specific *Metn1* knock-out (KO) mice that the lack of *Metn1* could reduce the immune cell infiltration. Moreover, this deficiency impeded the transition towards an anti-inflammatory phenotype, a process that is typically mediated through STAT3 activation.<sup>11</sup> Osteoactivin and *Metn1* have been revealed to have positive correlation in regulating bone cell differentiation.<sup>53</sup> This synergistic

interaction between Metrnl and osteoactivin underscores their critical involvement in the muscle-bone crosstalk. Moreover, research focusing on genes implicated in osteoblast differentiation revealed that Metrnl exhibits a distinctive expression pattern in bone, potentially inhibiting bone cell differentiation.<sup>17</sup> Collectively, these studies position Metrnl as a key regulator in immune inflammation and the muscle-bone crosstalk, and as a potential therapeutic target for conditions such as osteoporosis.

## Metrnl and Rheumatoid Arthritis

Rheumatoid arthritis (RA) represents a chronic, systemic autoimmune disorder predominantly manifesting as progressive inflammatory pathology within synovial joints. This condition is distinguished by a hallmark immune-mediated inflammation targeting synovial tissues, leading to the degradation of articular cartilage and subsequent osseous resorption. Clinically, RA is typified by symptoms such as persistent pain, synovial swelling, joint tenderness, rigidity, and progressive deformities of the affected joints. Epidemiologically, RA has a global prevalence impacting approximately 0.5% to 1% of the population, underscoring its significance as a major rheumatologic health concern. In the pathogenesis of this articular pathology, there is a pronounced synovial hyperplasia characterized by the infiltration and activation of immune cells, notably lymphocytes and macrophages, along with synovial fibroblasts. Concurrently, the synovium witnesses the formation of inflammatory cell conglomerates, predominantly composed of activated macrophages and lymphocytes, within the osseous marrow compartment. This immunopathological cascade precipitates synovitis, which is intricately associated with localized osteopenia, manifesting as a decrement in bone mineral density.<sup>54</sup> Metrnl is elevated in serum<sup>18</sup> and synovial membranes<sup>5,20</sup> of human rheumatoid arthritis. The investigation delineated a significant upregulation of serum Metrnl concentrations in patients with RA. These elevated levels of Metrnl exhibit a positive correlation with the Disease Activity Score 28 (DAS28), Rheumatoid Factor (RF), and C-Reactive Protein (CRP) levels. This correlation underscores Metrnl's involvement in the etiology and progression of RA.<sup>18</sup> Furthermore, the augmentation of serum Metrnl levels is intricately associated with the clinical activity of RA. This positions Metrnl not only as a crucial participant in the pathophysiological mechanisms of RA but also as a potential biomarker and therapeutic target for future interventions in RA management.

## Metrnl and Osteoarthritis

Osteoarthritis (OA) is recognized as a highly prevalent and progressively debilitating articular disorder, exerting a substantial impact on individual health and quality of life.<sup>55,56</sup> Recent evidence has redefined OA as a metabolic disorder, transcending the traditional view of it being merely a degenerative “wear and tear” arthritis.<sup>57,58</sup> While a myriad of pharmacological interventions are necessary to alleviate pain and enhance life quality in OA patients, none have demonstrated efficacy in arresting or reversing the disease's progression. Furthermore, these symptomatic treatments, often associated with adverse effects like nephrotoxicity and gastrointestinal complications, pose a significant economic burden over long-term usage.<sup>59,60</sup> Obesity is universally acknowledged as a primary and modifiable risk factor for the development of OA.<sup>61</sup> Recent research has shed light on the importance of Metrnl, an emerging adipokine, in the pathophysiology of OA. This novel adipokine has been identified to have significant associations with the onset and progression of OA, suggesting a potential mechanistic link between adipose tissue dysregulation and osteoarthritic changes.<sup>62</sup> Metrnl has been identified as a key agent in counteracting obesity-induced insulin resistance and enhancing glucose tolerance. This is predominantly mediated through the activation of PPAR $\gamma$ , a factor critical to the pathophysiology of OA. Activation of PPAR $\gamma$  exerts anti-inflammatory effects and diminish the synthesis of cartilage degradation markers, both in vitro and in vivo studies. Notably, PPAR $\gamma$  activation has also been associated with a reduction in the development of cartilage lesions in OA animal models.<sup>63</sup> A recent study delineated a distinctive pattern in the distribution of Metrnl levels among obese individuals with and without OA. Findings indicated that, in obese patients afflicted with OA, serum levels of Metrnl were observed to be lower compared to those in obese individuals without OA. Contrastingly, Metrnl concentrations were higher in the synovial fluid of OA patients. Additionally, a notable decrease in Metrnl levels was observed in serum of subjects with advanced-stage OA, as opposed to those with early-stage OA, suggesting a potential inverse correlation between Metrnl levels and OA severity.<sup>19</sup> Liu et al conducted pivotal research demonstrating that Metrnl mitigates inflammation through the inhibition of the PI3K/Akt/NF- $\kappa$ B signaling pathway in



IL-1 $\beta$ -stimulated OA chondrocytes. Additionally, Metrnl was shown to curtail chondrocyte pyroptosis by impeding the nod-like receptor protein-3 (NLRP3)/caspase-1/gasdermin D cascade.<sup>64</sup> These seminal findings not only position Metrnl as a promising therapeutic target for Osteoarthritis but also pave the way for further exploration into its mechanistic role in the pathology of OA.

## Metrnl and Axial Spondyloarthritis

Axial spondyloarthritis (AxSpa), known as ankylosing Spondylitis, is a chronic inflammatory rheumatic disease that often causes back pain and limited mobility. Assessing clinical manifestations and monitoring disease activity is important for early diagnosis and effective treatment. A study showed that the serum Metrnl concentration of AxSpa patients was lower compared with healthy individuals. However, the mechanism was still undiscovered. Metrnl as a novel biomarkers is related with autoimmune inflammatory rheumatic diseases, which could be used to measure clinical disease activity and assess treatment efficacy.<sup>65</sup>

## Metrnl and Elbow Stiffness

Elbow stiffness is a challenging and common problem in surgical treatment. Long-term joint fixation is generally recognized as a basic risk factor for posttraumatic motor disability. This pathological state precipitates a cascade of physical and biochemical dysfunctions within and surrounding joint structures. Key manifestations include the erosion of articular cartilage, a marked reduction in the content of articular proteoglycans, and the development of soft tissue contractures, particularly affecting the joint capsule.<sup>66,67</sup> Heterotopic ossification (HO) initiated by inflammation and the ectopic bone formation within soft tissues is the primary cause of elbow stiffness, Fan et al reported that the IL-17 plays a critical role in the formation of HO. At the early stage of HO, IL-17 overexpressed and released into the tissue, and enhanced ectopic bone formation.<sup>68</sup> Metrnl is confirmed to inhibit the production of IL-17 and attenuate the progress of inflammation,<sup>31</sup> which is a significant potential of Metrnl in the research and treatment of elbow stiffness. Limited mobility is the major symptom of elbow stiffness. However, numerous studies showed that exercise could promote the expression of Metrnl, which in return suppress the inflammation and fibrosis.<sup>25,64</sup> These persuasive evidences suggested that there may be an important link with Metrnl and elbow stiffness.

## Metrnl and Aseptic Loosening Cased by Periprosthetic Osteolysis

Aseptic loosening is a prevalent complication that frequently occurs after total joint arthroplasty, primarily attributed to periprosthetic inflammatory osteolysis. It stands as the primary cause for revision procedures.<sup>40</sup> The loosening of joint implants due to wear debris incurs a significant need for revision surgery, leading to severe complications and substantial economic burden.<sup>69</sup> The release of wear particles from the prosthetic materials triggers a persistent local inflammatory response, and inflammatory factors such as IL-1 $\beta$ , IL-6, TNF- $\alpha$ , RANKL and PGE2 were generated and secreted by macrophages, thereby stimulating osteoclast activities and resulting in bone loss around the implant.<sup>70</sup> Metrnl inhibited the secretion of TNF- $\alpha$ , IL-1 $\beta$  and other inflammatory factors and promoted the production of anti-inflammatory factors in macrophages, thus suppressed the inflammation response and osteolysis.<sup>5,32,37</sup>

## Metrnl and Muscle Injury

Sarcopenia, alongside other muscular injuries, represents a prevalent health concern, frequently resulting in significant disability, chronic pain, and an elevated economic burden.<sup>71</sup> Skeletal muscle possesses remarkable regenerative capabilities, and the interaction between muscle and the immune system during muscle repair is crucial for successful regeneration.<sup>72</sup> Baht et al confirmed Metrnl facilitate skeletal muscle repair.<sup>11</sup> Metrnl was high expressed in macrophages in the injured muscle, and in turn, Metrnl stimulated macrophages to produce growth factors functions in muscle regeneration through STAT3/IGF-1 signaling pathway.<sup>11</sup> Another research showed that the immune responsiveness is enhanced by Metrnl to counteract a pro-fibrotic program through inducing apoptosis of fibro/adipogenic progenitor (FAP), which improved muscle homeostasis and repair in aged muscle.<sup>73</sup> Obesity and metabolic disorders development are companied with skeletal muscle inflammation, which characterized by the activation of proinflammatory responses and the infiltration of immune cells in intramyocellular and perimuscular adipose tissues.<sup>74</sup> Several studies suggested that

exercise-induced Metrnl performed anti-inflammatory effects on by inhibiting NLRP3 inflammasome activation and downregulating the expression of pro-inflammatory cytokines.<sup>25,75</sup> Metrnl has anti-inflammatory and healing effects on skeletal muscle injury, suggesting a new therapeutic target on skeletal muscle inflammation.

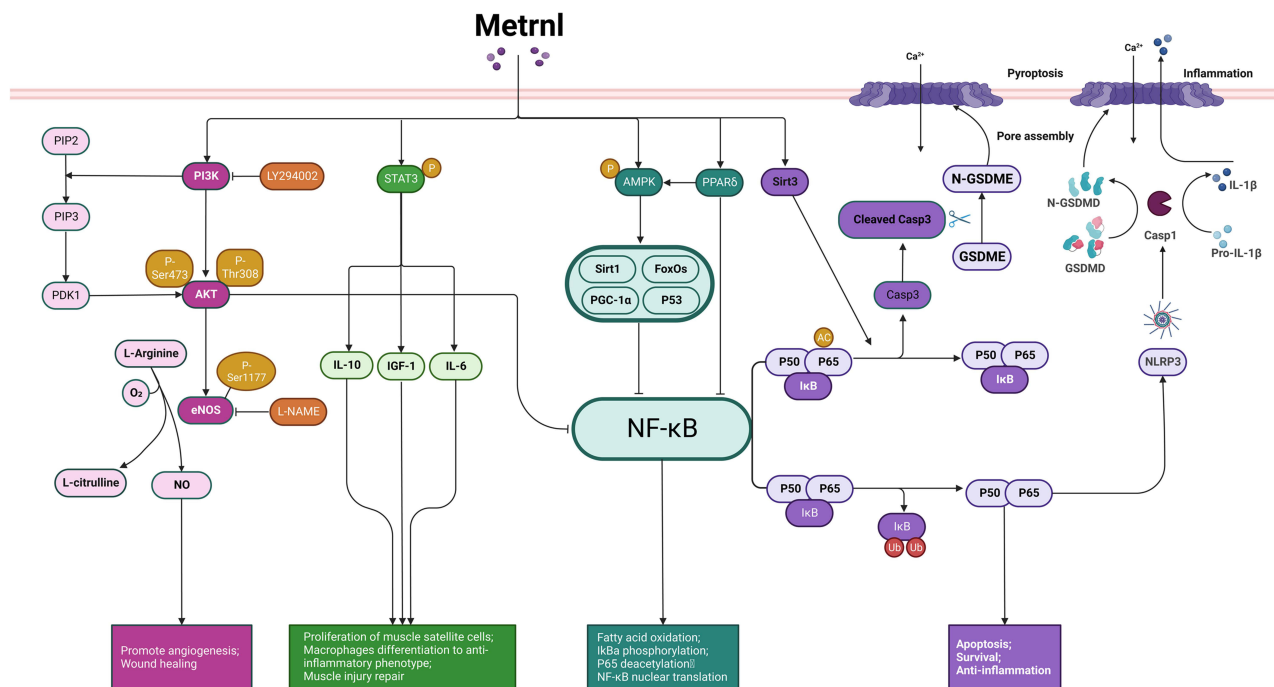
## Metrnl and Wound Healing

Skin wound healing is a complex process associated with endothelial-mediated angiogenesis and anti-inflammatory actions.<sup>76</sup> Impaired wound healing is a significant contributor to morbidity in patients with diabetes with increased inflammation and poor angiogenesis, often leading to foot ulcers, amputation, and even death.<sup>77,78</sup> Studies showed that Metrnl overexpressed and released by endothelial cells and then promoted the proliferation, migration and tube formation of endothelial cells through AKT/eNOS signal pathway.<sup>79,80</sup> Another study reported Metrnl overexpressed during the process of physiological wound healing, and thus promoted M2 macrophage polarization and increased endothelial cell proliferation. Activated M2 macrophages further secreted more Metrnl to promote angiogenesis, ultimately enhancing the repair of skin injuries.<sup>81</sup>

## Pathways of Metrnl Contributing to Anti-Inflammatory Effects

During the past years, Metrnl as a new adipokine has garnered considerable interest for its anti-inflammatory functions in various disorders.<sup>5,82</sup> Presently, Metrnl is also recognized for its significant role in the pathogenesis and progression of orthopedic diseases (Figure 2). It can influence these conditions by inducing or inhibiting catabolic or apoptotic pathways, and by directly or indirectly affecting bone metabolism.<sup>3,15,19</sup> However, the mechanism of Metrnl regulating anti-inflammatory responses and bone diseases is still unclear.

### Signaling Pathways in inflammatory-mediated pathological bone osteolytic diseases



**Figure 2** Signaling Pathways of Metrnl regulating inflammatory-mediated pathological bone osteolytic diseases. Created with BioRender.com.

**Abbreviations:** PI3K, phosphatidylinositol 3-kinases; eNOS, endothelial Nitric Oxide synthases; ROS, reactive oxygen species; STAT3, the signal transducer and activator of transcription family 3; AMPK, AMP-activated protein kinase; PPAR-γ, peroxisome proliferator-activated receptor-δ; NF-κB, nuclear factor κB; MMPs, matrix metalloproteinases; ADAMTS5, a disintegrin and metalloproteinase with thrombospondin motifs 5; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; GSDMD, gasdermin D; PGC-1α, peroxisome proliferator-activated receptor γ co-activator 1α.

## AKT/eNOS Signaling Pathway

Xu et al reported that Metrn1 participates skin wound healing by regulating angiogenesis through AKT/eNOS signaling pathway,<sup>79</sup> a key pathway downstream of angiogenic factors VEGFA, which can increase the production of NO(\*) in endothelial cell to promote angiogenesis.<sup>83</sup> In Metrn1-/- mice, the expression of VEGFA was suppressed and further inhibited the phosphorylation of p-AKT(S473) and p-eNOS(S1177) in HUVECs and skin wound tissues, leading to attenuated angiogenesis and consequently retarding wound healing. When Metrn1-deficient HUVECs were co-incubated with SC79, an AKT activator, a marked restoration in their angiogenic activity was observed.<sup>79</sup>

## PI3K/Akt/NF- $\kappa$ B Signaling Pathway

Nuclear factor  $\kappa$ B (NF- $\kappa$ B) plays a pivotal role in the pathogenesis of inflammatory-mediated pathological orthopedic diseases. Chronic activation of NF- $\kappa$ B in chondrocytes is a primary factor driving pathological changes in OA.<sup>84</sup> It was also involved in the process of trauma-induced HO development.<sup>85</sup> The PI3K/Akt signaling pathway activates NF- $\kappa$ B and facilitates its nuclear translocation through phosphorylation. It has been implicated to inducing inflammation in chondrocytes, accompanied by upregulation of matrix metalloproteinases (MMPs), a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5), as well as the decrease of collagen II.<sup>86</sup> Metrn1 exerts its anti-inflammatory effects by inhibiting the activation and nuclear translocation of NF- $\kappa$ B.<sup>64</sup> IL-1 $\beta$  induction increased the phosphorylation levels of PI3K, Akt, NF- $\kappa$ B p65, and I $\kappa$ B $\alpha$ . However, the administration of Metrn1 can suppress these changes, thereby mitigating inflammation and pyroptosis in OA chondrocytes.

## STAT3/IGF-I Signaling Pathway

Metrn1 directly signals to macrophages through STAT3 pathway, leading to their differentiation into an anti-inflammatory phenotype and induces expression and secretion of growth factor IGF-1 functioning on muscle regeneration.<sup>11</sup> When the muscle was injured, Metrn1 was high expressed in macrophage populations, which is crucial for muscle regeneration. Phosphorylation of STAT3 was increased in bone marrow-derived macrophages after Metrn1 treatment. Phosphorylated STAT3 further induced the expression of several growth factors (IL-6, IL-10 and IGF-1) in macrophages associated with muscle regeneration, which were eliminated by the STAT3 inhibitor. The secretion of IGF-1 stimulated the proliferation of muscle satellite cells, which is crucial for muscle regeneration.<sup>11</sup> Aberrant STAT3 signaling was experimentally linked to a wide range of intracellular processes.<sup>87</sup> In chondrocytes, STAT3 activation has been observed to induce degradation and apoptosis.<sup>88</sup> However, the interrelation of STAT3 with Metrn1 appears complicated and far from being fully elucidated.

## AMPK or PPAR $\delta$ -Dependent Pathways

AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor  $\delta$  (PPAR $\delta$ ) play pivotal roles in cellular energy homeostasis. AMPK phosphorylation and PPAR $\delta$  activation exert significant anti-inflammatory effects and immunosuppressive effects by suppressing the NF- $\kappa$ B signaling pathway.<sup>89,90</sup> Jung et al reported that Metrn1 could induce AMPK phosphorylation and PPAR $\delta$  expression independently and consequently decreased inflammation. In vivo experiments conducted on mice fed with a high-fat diet demonstrated that treatment with Metrn1 effectively mitigated NF- $\kappa$ B signaling and reduced the production of pro-inflammatory cytokines (TNF $\alpha$  and MCP-1).<sup>44</sup> In addition, Metrn1 increased the expression of peroxisome proliferator-activated receptor  $\gamma$  co-activator 1 $\alpha$  (PGC-1 $\alpha$ ) through AMPK and PPAR $\delta$ -mediated signaling.<sup>44</sup> PGC-1 $\alpha$  has been proved protective effects in muscle biology by suppressing chronic inflammation and muscle catabolism.<sup>91</sup> Another study confirmed that Metrn1 can suppress LPS-induced inflammation in HUVECs and THP-1 cells via AMPK and PPAR $\delta$ -mediated signaling pathways.<sup>32</sup> Treatment with Metrn1 on HUVECs, THP-1 cells, and primary mouse monocytes exhibited a concentration-dependent mitigation of LPS-induced phosphorylation of NF- $\kappa$ B and I $\kappa$ B, as well as the translocation of NF- $\kappa$ B into the nucleus. Furthermore, the administration of Metrn1 effectively attenuated the elevated levels of pro-inflammatory cytokines in HUVECs and THP-1 cells.<sup>32</sup> Metrn1 regulates AMPK or PPAR $\delta$ -dependent signaling pathway simultaneously, thereby suppressing inflammatory diseases.



## NLRP3/Caspase-1/GSDMD Signaling Pathway

Metn1 can regulate the activation of NLRP3 inflammasome and inhibit inflammatory response.<sup>25,64</sup> NLRP3 is a cytoplasmic immune factor in response to cellular stress signals. As a member of the NOD-like receptor family, it is normally activated in response to infection or inflammation, forming the NLRP3 inflammasome (composed of NLRP3, adapter protein ASC, and inflammatory protease caspase-1), which induces apoptosis.<sup>92</sup> Exercise-induced Metn1 could ameliorate pyroptosis in chondrocytes by inhibiting the NLRP3/caspase-1/GSDMD pathway. This leads to improved chondrocyte morphology and recovery of nuclear integrity.<sup>5</sup> Another research reported that exogenous Metn1 treatment suppressed NLRP3 inflammasome activation and completely abolished IL-1 $\beta$  secretion in BMDMs induced by LPS and ATP. Moreover, this effect was partly mediated by activation of both ERK and p38 MAPK signaling.<sup>93</sup> The NLRP3 inflammasome primarily functions in inducing gasdermin D (GSDMD)-dependent pyroptosis, significantly influencing the pathophysiology of OA.<sup>64</sup> Based on the aforementioned reports, it can be postulated that Metn1 represents a promising target for effectively attenuating NLRP3-mediated inflammation in adipose tissues. Consequently, this highlights its therapeutic potential in addressing metabolic and inflammatory disorders.

## Discussion and Future Perspectives

Metn1, as an emerging adipokine, plays a vital role in both pathological and physiological processes and shows regulatory functions in metabolic and inflammatory diseases.<sup>9,37</sup> This study reported the important link of Metn1 and skeletal development, remodeling, and some bone-related diseases, contributing to understanding the role of Metn1 in inflammatory orthopedic diseases and demonstrating its potential in orthopedic disease therapy.<sup>15</sup>

Metn1 has been proved to participate the development of orthopedic disease by regulating immune inflammation and bone-muscle crosstalk, including periprosthetic osteolysis, aseptic loosening, osteoporosis, rheumatoid arthritis and axial spondyloarthritis.<sup>64,73,82</sup> The expression of Metn1 can be induced by exercise, like elbow stiffness,<sup>25,64</sup> the mechanism of which is still indistinct. Metn1 regulates the expression of cytokines related to inflammation and fibrosis, which are participated in the regulatory pathway of heterotopic ossification and joint contracture, showing the potential of Metn1 in the occurrence of elbow stiffness. Exercise induced the production of Metn1 and it relieves the symptoms of elbow stiffness, further indicating it might be used in elbow stiffness therapy.

Despite clinical evidence linking Metn1 to a number of orthopedic inflammatory diseases, the function of Metn1 still require further validation, and its mechanisms are unexplored. Clinical investigations of Metn1 and possible orthopedic disorders remain inadequate. The function and mechanism of Metn1 in human orthopedic diseases continue to be areas needing more comprehensive exploration and understanding. More clinical studies are needed to verify the relationship between Metn1 and various orthopedic diseases and inflammatory diseases, as well as other underlying conditions that Metn1 may be involved in. This research will help improve our understanding of the role of Metn1 in human orthopedic health and disease.

In conclusion, these studies have prompted us to acknowledge the significant contribution of Metn1 in the pathogenesis and prevention of orthopedic conditions, particularly elbow stiffness. While the pathogenesis of elbow stiffness remains elusive, current literature suggests that Metn1 likely exerts a pivotal role in its development. However, the existing body of research remains insufficient to fully elucidate this phenomenon. The function and mechanism of Metn1 in the orthopedic diseases still need more investigation. More preclinical studies are essential to elucidate its molecular mechanisms, providing a stronger scientific foundation for its potential medical applications in the future.

## Funding

This work was partially supported by the Natural Science Foundation of Shandong Province (No. ZR2021QH307; No. ZR2023QH498; No. ZR2021MH013), the Shandong Province Major Scientific and Technical Innovation Project (No. 2021SFGC0502), and the Jinan Clinical Medical Science and Technology Innovation Plan (NO. 202328065). The authors, their immediate families, and any research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

# Disclosure

The authors report no conflicts of interest in this work.

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