Advances in selenium research for bone and joint-related diseases: from pathophysiological mechanisms to therapeutic implications of selenium-based biomaterials

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ABSTRACT

Selenium is an essential trace mineral crucial for human health. The selenium-selenoprotein axis exerts biological effects that are associated with bone and joint health. The metabolism of selenium in vivo involves multiple physiological mechanisms and organs working synergistically to maintain selenium homeostasis. Studies underscore the roles of selenium in diverse physiological processes, including antioxidant defense, anti-inflammatory responses, immune regulation, osteogenesis, and thyroid hormone metabolism. Conditions such as Kashin–Beck disease, rheumatoid arthritis (RA), osteoarthritis (OA), and osteoporosis have been linked to selenium deficiency. Adequate selenium supplementation has been shown to prevent and treat bone and joint-related diseases. While numerous natural and synthetic selenium compounds have been explored for their therapeutic potential in bone and joint-related diseases, their narrow therapeutic windows pose challenges. In recent years, selenium-based biomaterials have been extensively studied and applied in biomedical research. These biomaterials exhibit reduced toxicity and enhanced bioavailability compared to inorganic and organic selenium, making them promising strategies for targeted selenium delivery. Selenium-based biomaterials provide a more efficient alternative for the treatment of bone defects, osteoporosis, osteosarcoma, OA, RA, and other related diseases. This review highlights the pathophysiological functions of selenium in maintaining bone and joint homeostasis and summarizes the current progress in utilizing selenium-based biomaterials for treating bone and joint-related diseases.

Keywords:
Selenium; Selenoproteins; Bone and joint-related diseases; Selenium nanoparticles; Therapeutics

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1. Introduction

Selenium is an essential trace mineral involved in the synthesis of selenoproteins and plays an important role in human physiological functions.[1] Selenium, discovered by Jons Jacob Berzelius in 1817, has undergone significant transformation over the past two centuries. Initially considered a "malignant poison," it was later recognized in the mid-1950s as an "important protective factor against diet-induced hepatic necrosis".[2] Today, selenium is widely regarded as a "longevity element", the "king of anti-cancer", and the "guardian of health", with its importance becoming increasingly prominent. Selenium is the only trace element included in the genetic code, as the 21st amino acid, selenocysteine (Sec).[3] Selenoproteins are the primary form of selenium in the body.[4] The human genome encodes 25 selenoprotein genes, including glutathione peroxidases (GPxs), thioredoxin reductases (TrxRs), and iodothyronine deiodinases (DIOs).[5] Selenium and its selenoproteins play crucial physiological roles in antioxidant defense, inflammation regulation, DNA repair, immune system modulation, protection against

pathogenic microorganisms, and cancer prevention, thereby promoting overall health.[3, 6-8] Notably, selenium is essential for the enzymes involved in the synthesis and metabolism of thyroid hormones. Selenium supplementation in adequate amounts has been shown to positively promote thyroid function and immune cell activity.[9] In terms of immunomodulation, selenium exhibits significant immunostimulatory effects, including improving T cell proliferation, activating natural killer cells, and enhancing tumor cell cytotoxicity mediated by cytotoxic lymphocytes.[10,11] Beyond its general physiological and immune functions, selenium deficiency is linked to various diseases, including Keshan disease, cancer, liver disease, and arthropathy.[12-17] Given its broader impact on systemic health, selenium's relationship with bone and joint health warrants further investigation.

Bone and joint homeostasis is a complex process regulated by numerous factors and signaling pathways. These structures also serve as important reservoirs for various metallic and non-metallic components, cytokines, and growth factors. Selenium is essential for maintaining physiological bone homeostasis.[18] Several studies have demonstrated that selenium supplementation can regulate the production of selenoproteins in osteoblasts, sustain redox balance, enhance bone metabolism, and increase bone density.[19, 20] Conversely, selenium deficiency can lead to abnormal bone metabolism, causing Kashin–Beck disease (KBD), while exogenous selenium supplementation helps maintain bone homeostasis and promotes bone regeneration after injury.[21] In recent years, the relationship between selenium and osteoarthritis (OA) has attracted considerable attention. Studies have shown a significant association between selenium levels and the symptomatic manifestations and severity of OA.[22] A large population-based cross-sectional survey revealed that plasma selenium concentrations are negatively correlated with the occurrence of radiographic OA in the knee, hip, or hand.[16] In addition, selenium metabolism plays an important part in cartilage homeostasis and bone development. Selenium deficiency can result in numerous bone and joint-related diseases, such as OA and KBD.[18] Selenium deficiency increases type X collagen expression and parathyroid hormone-related peptide (PTHrP), with type X collagen serving as a marker for chondrocyte hypertrophy in articular cartilage, and PTHrP regulating chondrocyte maturation in both articular cartilage and hypertrophic growth plates. Due to increased bone metabolism, PTHrP also contributes to bone resorption and the retardation of bone growth.[22,23] Therefore, exploring the function of selenium in articular cartilage and subchondral bone degeneration may offer novel strategies for the treatment of OA.

Studies have shown that the body's selenium needs are frequently unmet due to low selenium levels in diets. Conventional selenium supplements are often poorly absorbed and may be toxic. Recent advancements in functional biomaterials have provided innovative strategies for treating bone and joint-related diseases.[24-27] The development of selenium-based biomaterials is critical for improving selenium bioavailability and achieving controlled release of selenium in living organisms.[28] Nanomaterials, with their unique physicochemical properties, have gained significant attention in fields such as applied physical chemistry, biomedicine, and mechanical engineering.[29] Nano-sized selenium shows better antioxidant activity and reduced toxic effects compared to conventional selenium.[30] Selenium nanoparticles (SeNPs) have shown promise in treating a range of diseases, including diabetes, cancer, and inflammation-related diseases. SeNPs can function either directly or by doping with selenoproteins. Depending on the therapeutic requirement, SeNPs can be administered through several routes, such as oral and intravenous delivery.[31] Recent studies have revealed the therapeutic benefits of SeNPs in treating bone and joint-related diseases, including bone defects, osteoporosis, and OA.[32-34] SeNPs promote mesenchymal stem cell differentiation into osteoblasts by regulating oxidative stress.[20] Therefore, in-depth studies on low-toxicity, efficient SeNPs and their mechanisms of action may provide pathways for addressing several human health concerns.

Based on previous research, this review explores the mechanisms of selenium's action in bones and joints. We focus on the progress made in conventional selenium compounds compared to selenium-based biomaterials for treating bone and joint-related diseases. In addition, we outline promising future research directions aimed at optimizing selenium-based therapies to enhance efficacy and minimize side effects. Overall, the development of novel selenium-based biomaterials with targeted delivery capabilities presents significant potential for advancing strategies in the treatment of osteoarticular diseases.

2. Selenium metabolism and pathophysiological functions of selenoproteins

2.1. Systemic selenium metabolism and homeostasis regulation in organisms

Given that the human body cannot synthesize selenium independently, its intake relies almost entirely on dietary sources, including seafood, grains, legumes, meat products, and vegetables.[35,36] The World Health Organization recommends a daily intake of 55 μg.[37] The proposed ideal concentration of selenium in plasma is 90 to 120 μg/L, which is sufficient to saturate selenoproteins in the blood.[38] Selenium in food exists in both organic and inorganic forms. Organic selenium includes selenomethionine (SeMet) and Sec, whereas inorganic selenium comprises selenite, selenide, selenate, and other selenium compounds.[39] Organic selenium is primarily absorbed in the duodenum and cecum through the active transport mechanism

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of the sodium pump.[39] Inorganic forms are selectively absorbed by erythrocytes.[40] Each form can be converted into selenide, which is a key step in the synthesis of Sec.[41]

The adult human body contains approximately 20 mg of selenium, with 30% stored in the liver, 30% in muscle, 15% in the kidneys, 10% in plasma, and the remaining 15% distributed across other organs.[42] Selenium balance in the body is primarily maintained through reserves of SeMet in the kidneys and liver. When dietary selenium intake falls below the requirement for selenoprotein synthesis, the stored selenium is mobilized for use.[43] In cases of excessive selenium levels, it is excreted as small-molecule metabolites through urine and feces.[44] Urinary selenium is primarily found in the forms of selenate, methylselenide, and Sec, whereas fecal selenium mainly comes from unabsorbed dietary selenium and biliary excretion. Once fecal excretion reaches saturation, selenium is also excreted through respiration and increased urinary excretion.[3] These excretion mechanisms help prevent excessive selenium accumulation and maintain selenium homeostasis in the body (**Figure 1A**). In summary, the intake, absorption, transport, storage, excretion, and balance regulation of selenium in the body involves multiple physiological mechanisms and organs working synergistically to maintain selenium homeostasis and optimize its biological effects.

2.2. Intracellular synthesis of selenoproteins

Selenium is absorbed from food and undergoes multiple translational processes before being integrated into the polypeptide chain to complete selenoprotein synthesis. Selenium is co-translationally integrated into the polypeptide chain as the amino acid Sec.[4] Sec is synthesized universally on its transfer RNA (tRNA) through a serine intermediate, unlike the other 20 amino acids encoded by the genetic code.[4] Inorganic forms of selenium are reduced by the thioredoxin/TrxR (Trx/TrxR) system or the GPx redox (glutathione/glutathione reductase) system, while organic forms are cleaved by Sec lyase, resulting in the synthesis of hydrogen selenide.[18] Selenide is then reduced to selenophosphate by selenophosphate synthetase 2,[13] which subsequently interacts with phosphoserine-tRNA$^{Ser]Sec}$ to produce selenocysteyl (Sec)-tRNA$^{Ser]Sec}$.[45] Sec-tRNA$^{Ser]Sec}$ transfers Sec to newly formed selenoproteins co-translationally, through cis-acting Sec insertion sequence (SECIS) elements present in the selenoprotein messenger RNA and trans-acting factors, including SECIS-binding protein 2 (SBP2), selenophosphate synthetases (SEPHSs), and others.[46-48] In summary, the selenoprotein translation machinery comprises the SECIS element, SBP2, Sec-specific eukaryotic elongation factor, and aminoacylated Sec-tRNA$^{Ser]Sec}$, which allows the recognition of UGA as a Sec codon, enabling it to be translated into growing polypeptides.[4] The liver synthesizes selenoprotein P to supply selenium to other organs, where it is utilized to generate additional selenoproteins to perform various physiological functions (**Figure 1B**).[49]

2.3. Physiological properties of selenoproteins in organisms

Selenium exerts its biological effects by synthesizing selenoproteins.[38] Selenoproteins are a class of proteins containing Sec amino acid residues. All selenium within selenoproteins is located in active centers such as Sec, enabling them to perform physiological functions, such as antioxidant, anticancer, antidiabetic, anti-inflammatory, and osteogenic effects. A total of 24 selenoproteins have been discovered in mice.[50] To date, 25 selenoprotein-coding genes have been identified in the human genome,[5] including those that encode GPx, TrxRs, DIOs, SEPSHS2, methionine-R-sulfoxide reductase 1, and selenoprotein H, I, K, M, N, O, P, R, S, T, V, and W.[5, 51, 52] The specific expression of these selenoproteins in tissues can be regulated by hormones.

GPx was the first identified selenoprotein. In humans, five types of Sec-containing GPxs have been described.[50] GPx1 and GPx4 reportedly inhibit phosphorylation cascades by preventing the oxidative inactivation of phosphatases, primarily through the elimination of hydrogen peroxide (H_2O_2) or lipid hydroperoxides.[53] GPx2 regulates the balance between apoptosis-induced shedding and regeneration of intestinal cells.[54] GPx3 deficiency may promote platelet aggregation by deregulating the inhibition of thromboxane biosynthesis.[55] Studies have shown that the cytoplasmic form of GPx4 can inhibit interleukin (IL)-1-driven activation of nuclear factor kappa B (NF-κB) and the biosynthesis of leukotrienes.[53]

There are three selenoproteins in the DIO enzyme system: DIO1, DIO2, and DIO3. Their main physiological function is to regulate thyroid hormone bioactivity by controlling the levels of thyroxine (T4) and the active hormone 3,3',5'-triiodothyronine (T3).[56, 57] DIO1 and DIO2 facilitate the conversion of T4 into the active thyroid hormone T3,[58] whereas DIO3 changes T4 into the inactive reverse-T3 (rT3) and T3 into T2.[5] DIO1 and DIO2 can also convert reverse T3 into 3,3'-diidothyronine.[59]

The TrxR enzyme system is composed of TrxR1, TrxR2, and TrxR3. In addition to their antioxidant functions, TrxRs also participate in cell proliferation and apoptosis.[60] Their key physiological function is to help maintain selenium micronutrient status by catalyzing the reduction of disulfide bonds in oxidized thioredoxin through the catalytic power of nicotinamide adenine dinucleotide phosphate.[61] Besides these functions, TrxRs bind to many cellular proteins, such as apoptosis signal-regulated kinase 1, and thus play a significant role in regulating cellular growth and inhibiting apoptosis.[60]

Importantly, additional selenoproteins have been discovered and cloned. Selenoprotein P, for instance, is a selenoprotein containing multiple Sec residues (a total of 10) in each protein subunit. It functions to transport selenium to various tissues and maintain cellular selenium homeostasis.[62] Selenoprotein K is expressed primarily in the heart and skeletal muscle and is involved in calcium metabolism.[4] Furthermore, selenoprotein N has been associated with myogenesis.[63] Defective expression or function of selenoproteins has been linked to a wide range of physiological disorders, including those affecting the muscular, skeletal, respiratory, neurological, and endocrine systems.[64]

3. The role of selenium and selenoproteins in bone and joint-related diseases

3.1. Oxidative stress coordination

Selenium and its associated selenoproteins play a critical role in maintaining redox homeostasis and protecting against

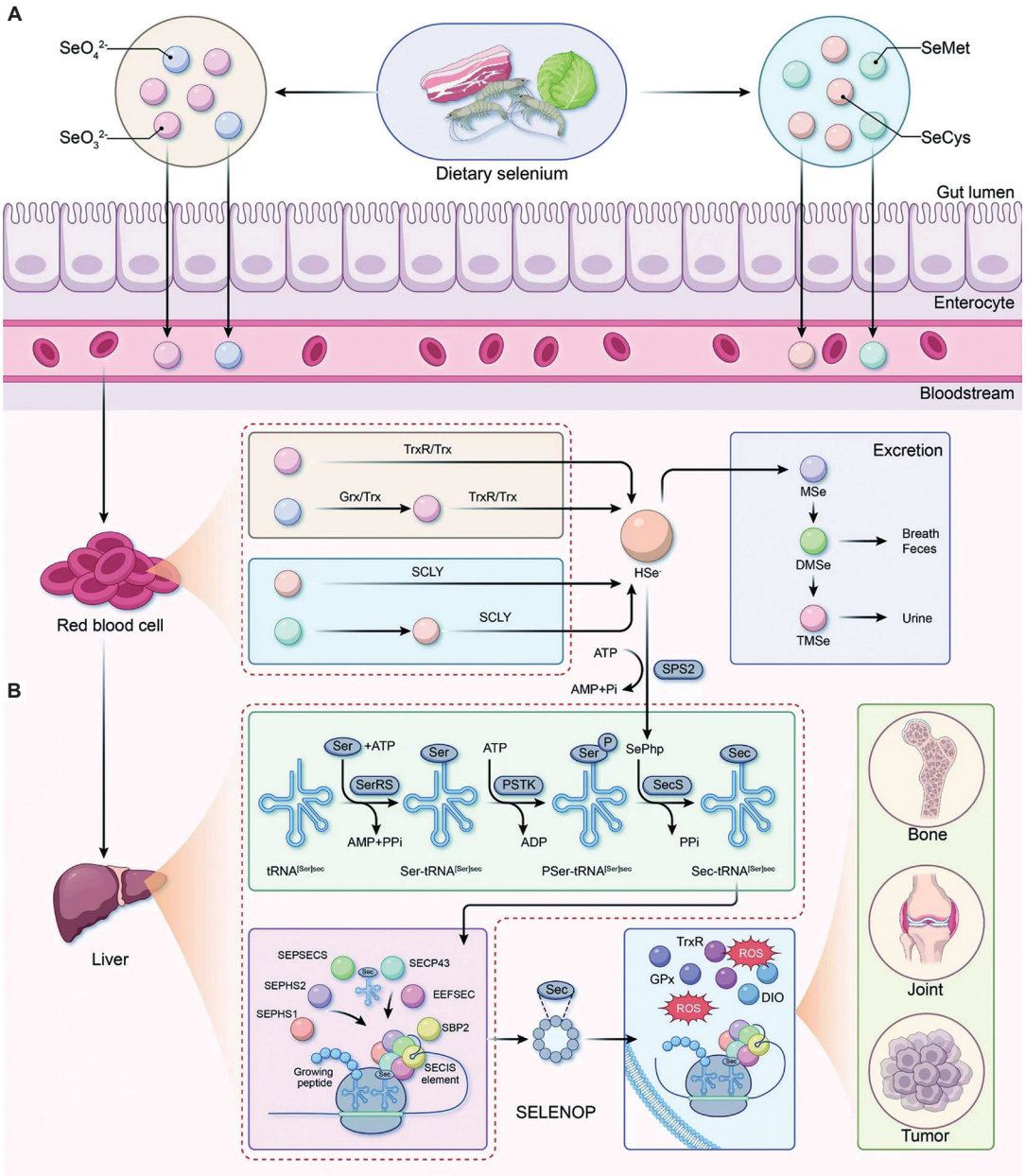

Figure 1. Selenium metabolism. (A) Systemic metabolism of selenium in organisms. Dietary sources of selenium uptake include inorganic forms such as selenate and selenite, as well as organic forms such as SeCys and SeMet. The absorption of selenium species occurs mainly in the small intestine through different routes. Selenium is quickly absorbed by red blood cells after intestinal uptake. Inorganic forms are reduced by TrxR, Trx, or Grx systems, while organic forms are cleaved by SCLY, forming selenide. Excess selenium is detoxified through a sequential methylation process into DMSe, which is excreted through breath and feces, and TMSe, which is excreted in the urine. (B) Synthesis of selenoproteins. Selenophosphate is synthesized from selenide by SPS2. The $tRNA^{Ser]Sec}$ is initially aminoacylated with serine by SerRS. Subsequently, PSTK transforms Ser-$tRNA^{Ser]Sec}$ into PSer-$tRNA^{Ser]Sec}$. Finally, SecS exchanges the phosphate group with activated SePhp to form Sec-$tRNA^{Ser]Sec}$. Sec-$tRNA^{Ser]Sec}$ is used to transfer Sec into nascent selenoproteins co-translationally through a mechanism that requires several dedicated cis-elements present in the selenoprotein mRNA (SECIS element), and protein factors that act in trans, including SBP2, EEFSEC, SEPHSs, and others. Finally, the UGA codon is recognized as the Sec integration codon. The liver synthesizes SELENOP to supply selenium to other organs, where additional selenoproteins can be synthesized. In bone, joint, and tumor tissues, selenoproteins perform unique physiological functions. The figure was created by authors using Adobe Illustrator.

Abbreviations: ADP: Adenosine diphosphate; AMP: Adenosine monophosphate; ATP: Adenosine triphosphate; DIO: Iodothyronine deiodinase; DMSe: Dimethylselenide; EEFSEC: Eukaryotic elongation factor, selenocysteine-tRNA specific; GPx, glutathione peroxidase; Grx: Glutathione reductase; HSe^-: Selenide; MSe: Methylselenide; P: Phosphate; Pi: Inorganic phosphate; PPi: Pyrophosphate; PSer-$tRNA^{Ser]Sec}$: Phosphoseryl-$tRNA^{Ser]Sec}$; PSTK: Phosphoseryl-tRNA kinase; ROS: Reactive oxygen species; SBP2: SECIS binding protein 2; SCLY: Selenocysteine lyase; Sec: Selenocysteine; SECIS: Selenocysteine insertion sequence; SECP43: SECIS-binding protein 43 kDa; SecS: Selenocysteine synthase; SeCys: Selenocysteine; Sec-$tRNA^{Ser]Sec}$: Selenocysteyl $tRNA^{Ser]Sec}$; SELENOP: Selenoprotein P; SeMet: Selenomethionine; SePhp: Selenophosphate; SEPHS1: Selenophosphate synthetase 1; SEPHS2: Selenophosphate synthetase 2; SEPSECS: Selenocysteine synthase; Ser: Serine; SerRS: Seryl-tRNA synthetase; Ser-$tRNA^{Ser]Sec}$: Seryl-$tRNA^{Ser]Sec}$; SeO_3^{2-}: Selenite; SeO_4^{2-}: Selenate; SPS2: Selenophosphate synthetase 2; TMSe: Trimethylselenide; tRNA: Transfer RNA; Trx: Thioredoxin; TrxR: Thioredoxin reductase.

bone and joint diseases, including OA and osteoporosis. Selenium enhances antioxidant defense mechanisms through selenoproteins such as GPxs and TrxRs,[65] which promote the development of cartilage precursor cells, prevent chondrocyte and cartilage matrix degradation, and protect chondrocytes from oxidative damage.[66] In addition, evidence suggests that selenoprotein S protects cells from oxidative damage by influencing immune and inflammatory signaling pathways.[67] Apoptosis is a common mechanism contributing to cartilage destruction in KBD,[68] and the phosphatidylinositol 3-kinase (PI3K) pathway, along with its downstream protein kinase B (Akt) kinase, plays an important role in regulating cell survival and apoptosis.[69] Studies have shown that individuals with severe osteochondrosis exhibit increased protein expression levels of G beta-gamma complex, PI3Kp110, phosphorylated Akt, and phosphorylated glycogen synthase kinase-3 compared to controls. Moreover, selenium has a significant protective effect on chondrocyte apoptosis by downregulating the PI3K/Akt signaling pathway. The four proteins mentioned above demonstrated greater expression levels in the C28/I2 human chondrocytes compared to the control group, but their expression was downregulated in the selenium-supplemented group.[70] In addition to KBD, reactive oxygen species (ROS) have also been implicated in the pathogenesis of osteoporosis. In osteoporosis, high intracellular ROS levels, resulting from a loss of mitochondrial function, inhibit the osteoblastic differentiation of bone marrow stem cells (BMSCs).[71-73] In OA, downregulation of SEPHS1 impairs selenoprotein synthesis, leading to elevated ROS levels and accelerated chondrocyte senescence.[74] Cartilage-specific *Sephs1* knockout mice showed exacerbated aging-associated and post-traumatic OA, and selenium deficiency further aggravated OA pathogenesis. These findings highlight SEPHS1 as a key regulator of selenium metabolism and redox homeostasis. Selenium, particularly in the form of sodium selenite, has been shown to restore osteogenic potential and mitochondrial function in BMSCs by upregulating GPx1 expression and reducing ROS levels.[75] In ovariectomized (OVX) rat models, selenium-modified bone cement promoted osteoporotic bone healing, suggesting GPx1 as a potential therapeutic target for osteoporosis.

3.2. DNA damage and repair

Chronic DNA damage induces chondrocytes to undergo apoptosis or cellular senescence.[76] Selenium has the potential to reduce DNA damage and enhance DNA repair.[77] Cancer cells supplemented with selenium (30 nM sodium selenite or 10 μM SeMet) exhibited increased GPx1 and TrxR1 enzyme activity levels, effectively preventing ultraviolet (UV) A- or H_2O_2-induced DNA strand breaks.[78] SeMet promoted the formation of repair complexes in DNA-damaged cells exposed to UV radiation, reducing DNA damage and enhancing repair.[79] Selenium protects DNA from damage by activating redox factor 1 (Ref1), which interacts with p53 and reduces crucial cysteine residues. Ref1, also known as apurinic/apyrimidinic endonuclease 1, is a key enzyme in the base excision repair pathway.[80] Selenium enhances Ref1 activity by modulating its redox state, which is critical for its function in DNA repair. Specifically, selenium likely promotes the reduction of Ref1's cysteine residues (Cys65 and Cys93), enabling its interaction with transcription factors such as p53 and NF-κB.[81, 82] This interaction facilitates the repair of oxidative DNA damage and enhances cellular survival.[83] Cells treated with SeMet demonstrated considerably increased DNA repair capacity upon exposure to various DNA-damaging agents (e.g., UV radiation or cisplatin treatment).[84] The trace element selenium reverses DNA damage and improves DNA repair capacity in response to various damaging environments, such as UV radiation or tumors. This was achieved through the formation of repair complexes in DNA-damaged cells, reducing the extent of DNA damage and enhancing the repair process. Considering its role in DNA damage repair, selenium may offer potential benefits for OA patients.

Selenium's DNA repair mechanism may stem from its vital role in the formation of selenoproteins such as GPxs and TrxRs, which are crucial for oxidative defense. Beyond its antioxidant properties, selenium can protect against DNA damage by activating pathways involving tumor protein p53 and breast cancer gene 1 (BRCA1).[85] BRCA1 is a protein involved in DNA damage repair. Selenium supplementation enhances the connection between BRCA1 and p53, and BRCA1 is essential for selenium' protective effects against UV-induced toxicity or DNA damage.[77]

3.3. Inflammatory stimulation remission

Selenium exhibits significant protective effects in bone and joint inflammation. SEPHS1 is a key regulator of the selenium metabolic pathway, and its absence may contribute to chronic inflammation within the joint environment.[74] *In vitro* experiments have demonstrated that selenium can alleviate IL-1β-induced chondrocyte inflammatory responses.[58,86] In addition, selenium inhibits the inflammatory response triggered by lipopolysaccharide in macrophages by modulating cytokine-induced nitric oxide synthase (iNOS) activity.[87] SeMet has been shown to inhibit IL-1β-induced iNOS and cyclooxygenase-2 gene expression in chondrocytes by attenuating the activation of the p38 mitogen-activated protein kinase (MAPK) pathway, thereby decreasing nitric oxide (NO) and prostaglandin production.[86] These findings suggest a putative protective mechanism of selenium by altering cell signaling and the downstream transcription of pro-inflammatory effects induced by IL-1β.

Macrophages play a crucial role in inflammatory osteolysis and are activated in two polarized states: the M1 and M2 phenotypes. When exposed to inflammatory stimuli, macrophages shift toward the M1 phenotype, releasing pro-inflammatory cytokines such as IL-6 and tumor necrosis factor-alpha. These cytokines enhance osteoclast activity and disrupt the osteogenic process.[88] Conversely, M2 macrophages are activated by IL-4 or transforming growth factor beta and produce IL-10 and IL-4, which reduce inflammation, enhance tissue repair, and restore function.[89, 90] Selenium has been shown to polarize macrophages toward the anti-inflammatory M2 phenotype by inhibiting the signaling pathways of p65, p38, and extracellular signal-regulated kinase (ERK), thereby enhancing the anti-inflammatory functions of macrophages.[91]

3.4. Anti-infection in bone and joint diseases

Selenium has emerged as a promising agent for addressing infections associated with bone and joint-related diseases, particularly in the context of orthopedic implants and traumatic injuries, where bacterial infections remain prevalent and have significant complications.[92,93] Recent advancements highlight selenium's antibacterial properties, demonstrating its efficacy against a broad spectrum of bacteria.[94,95] Several studies have shown that selenium-based biomaterials exhibit both antimicrobial and osteogenesis-promoting properties.[20,96,97] indicating the potential application of SeNPs in the treatment of infectious bone defects. Selenium supplementation has been found beneficial in treating infections caused by various bacteria, including *Helicobacter pylori*, *Escherichia coli*,[98] methicillin-resistant *Staphylococcus aureus*, and *Mycobacterium tuberculosis*.[98] Notably, selenium has also shown promise in managing opportunistic infections in patients with human immunodeficiency virus.[22] Selenium-based biomaterials have exhibited high bacteriostatic activity against Gram-negative bacteria (*E. coli*, *Salmonella* Typhimurium) and Gram-positive bacteria (*S. aureus*).[99] The antibacterial mechanisms involve altering bacterial membrane permeability, generating ROS, and inhibiting biofilm formation. Among these, selenium inhibits the growth of *S. aureus* through processes linked to the consumption of intracellular free thiols.[100,101]

3.5. Regulation of osteoblast, osteoclast, and chondrocyte differentiation

Bone development and maintenance are complex processes intricately regulated by the differentiation and activity of osteoblasts, osteoclasts, and chondrocytes. Emerging evidence has highlighted the pivotal role of selenium and selenoproteins in these regulatory mechanisms. For example, the polymorphism rs28665122 in the promoter region of selenoprotein S has been implicated in both an elevated risk of KBD and the upregulation of the PI3K/Akt signaling pathway, which is pivotal in chondrocyte apoptosis.[70] In a study examining tert-butyl hydroperoxide-induced chondrocyte apoptosis, selenium supplementation through sodium selenite treatment mitigated apoptosis by inhibiting this pathway.[102] Furthermore, targeted deletion of the Sec-tRNA$^{Ser]Sec}$ gene in embryonic osteochondral progenitor cells results in selenoprotein depletion in the skeletal system, leading to growth retardation, epiphyseal growth plate abnormalities, delayed endochondral ossification, and cartilage necrosis – key pathological features of KBD.[103] Several studies have shown that adequate selenium levels are essential for maintaining cartilage homeostasis, and selenium deficiency hinders cartilage and bone growth.[22,23] Selenium deficiency interferes with the chondrogenic differentiation of ATDC5 cells by inhibiting the expression of the chondrogenic genes such as SRY-box transcription factor 9, type II collagen, and aggregated proteoglycans, while also reducing alkaline phosphatase activity.[104] However, selenium deficiency can also lead to an increase in PTHrP expression. PTHrP stimulates the proliferation and hypertrophy of chondrocytes during osteogenesis in articular cartilage and hypertrophic growth plate cartilage and delays the terminal differentiation of chondrocytes during endochondral ossification.[105,106] Studies have shown that selenium deficiency leads to an increase in PTHrP expression in the intermediate zone of rat articular cartilage and the hypertrophic zone of the growth plate, a finding consistent with the cartilage abnormalities in KBD.[23]

Abnormalities in bone remodeling can lead to various bone diseases. For instance, overactivation of osteoclasts can result in conditions such as osteoporosis, metastatic bone cancer, and rheumatoid arthritis (RA).[107,108] Recently, Kim's team[109] discovered that the selenoprotein W (SELENOW), which incorporates selenium in the form of Sec, is essential for bone remodeling. Inhibition of SELENOW suppressed osteoclast differentiation, thereby alleviating osteoporosis caused by osteoclast overactivity. Through large-scale messenger RNA profiling, SELENOW was identified as a key protein downregulated through the receptor activator of nuclear factor kappa-B ligand/receptor for RANK-ligand/TNF receptor-associated factor 6/p38 signaling pathway during osteoclastogenesis. SELENOW modulates osteoclastogenic genes and influences the nuclear translocation of NF-κB and nuclear factor of activated T cells 1, mediated by 14-3-3γ, thereby enhancing osteoclast formation and bone resorption. *In vivo* studies have shown that SELENOW deficiency leads to a high bone mass phenotype, while its overexpression results in osteoporosis, highlighting its role in maintaining bone homeostasis. Notably, selenium deficiency-induced growth retardation may also be linked to abnormalities in bone metabolism.[22] According to research by Cao *et al.*,[110] increased bone resorption caused by selenium deficiency significantly impairs bone microarchitecture. This finding indicates that selenium deficiency not only affects chondrocyte and osteoblast differentiation but also disrupts the delicate balance between bone formation and resorption, leading to abnormal bone structure and function.

3.6. Osteoimmune regulation

Selenium has demonstrated potential anticancer activity both *in vivo* and *in vitro*. Inorganic and organic selenium compounds induce cell cycle arrest, cytotoxicity, and apoptosis in various cancer cell lines derived from colon, lung, or breast tissues.[111] Selenoproteins play significant roles in preventing tumorigenesis, inhibiting tumor growth, and promoting cancer cell apoptosis. While the antitumor effects of selenium are well-established, the precise mechanisms underlying these effects remain incompletely understood. Recent studies have identified GPx3 as a tumor suppressor, specifically inhibiting the proliferation and invasiveness of hepatocellular carcinoma and lung cancer cells.[112,113] Mechanistically, GPx3 protects MAPK, an ERK-specific phosphatase, from oxidative degradation, thereby blocking the ERK-NF-κB pathway.[114] Selenium may also function as an immunostimulant, reversing immunosuppression in the tumor microenvironment and promoting antitumor immunity by activating immune cells, such as M1 macrophages and cluster of differentiation (CD) 8^+ T lymphocytes, while inducing the release of proinflammatory cytokines, such as interferon-γ. Research in patients with giant cell tumors of bone has noted high GPx1 expression and elevated p53 levels,[115] leading to the hypothesis that selenium's antitumor effects may stem from a combination

of mechanisms, including its antioxidant, detoxification, and immune-enhancing properties (**Figure 2**).[116]

4. Therapeutic applications of selenium-based biomaterials in bone and joint diseases

4.1. Bone defects

In clinical practice, effectively repairing bone defects – common conditions resulting from factors such as infection, tumor, trauma, osteoporosis, surgical procedures, and congenital deformities[117] – remains a significant clinical challenge and a focal point of research.[118] Autologous bone grafting has been regarded as the gold standard for repairing bone defects.[119] While autografts have demonstrated excellent results in promoting bone healing, their limited availability and the complexity of surgical procedures hinder widespread application.[120] Allogeneic bone grafting, although addressing the source limitation, carries risks such as immune rejection, disease transmission, and high costs.[121] In this context, bone regeneration biomaterials, particularly those incorporating selenium, have emerged as a promising research area.[122, 123] Traditional metal implants, such as titanium alloys and cobalt-chromium-molybdenum alloys, offer excellent mechanical strength but are susceptible to *in vivo* corrosion.[124-126] Corrosion products from these implants can adversely affect surrounding tissues and may even pose carcinogenic risks.[127] In contrast, selenium plays a crucial role in bone regeneration (**Table 1** and **Figure 3**).[128, 129] For example, Rao *et al.*[130] combined the antioxidant effects of SeNPs with tanshinone IIA and astragalus polysaccharides (TSIIA@SeNPs-APS) (**Figure 4Aa**). This combination demonstrated significant efficacy in antioxidant therapy during bone regeneration associated with spinal cord injury. Analysis of footprints and hindlimb function revealed marked improvements in coordinated motor functions, re-establishment of upright posture, increased weight-bearing capacity, and recovery of joint range of motion in the TSIIA@SeNPs-APS group (**Figure 4Ab** and **c**). Furthermore, hematoxylin and eosin staining, Nissl staining, and terminal nucleotidyl transferase-mediated dUTP-biotin nick end-labeling/4',6-diamidino-2-phenylindole double-staining of TSIIA@SeNPs-APS-treated spinal cord injury rats indicated significant reductions in neuronal damage and apoptosis (**Figure 4Ad**).

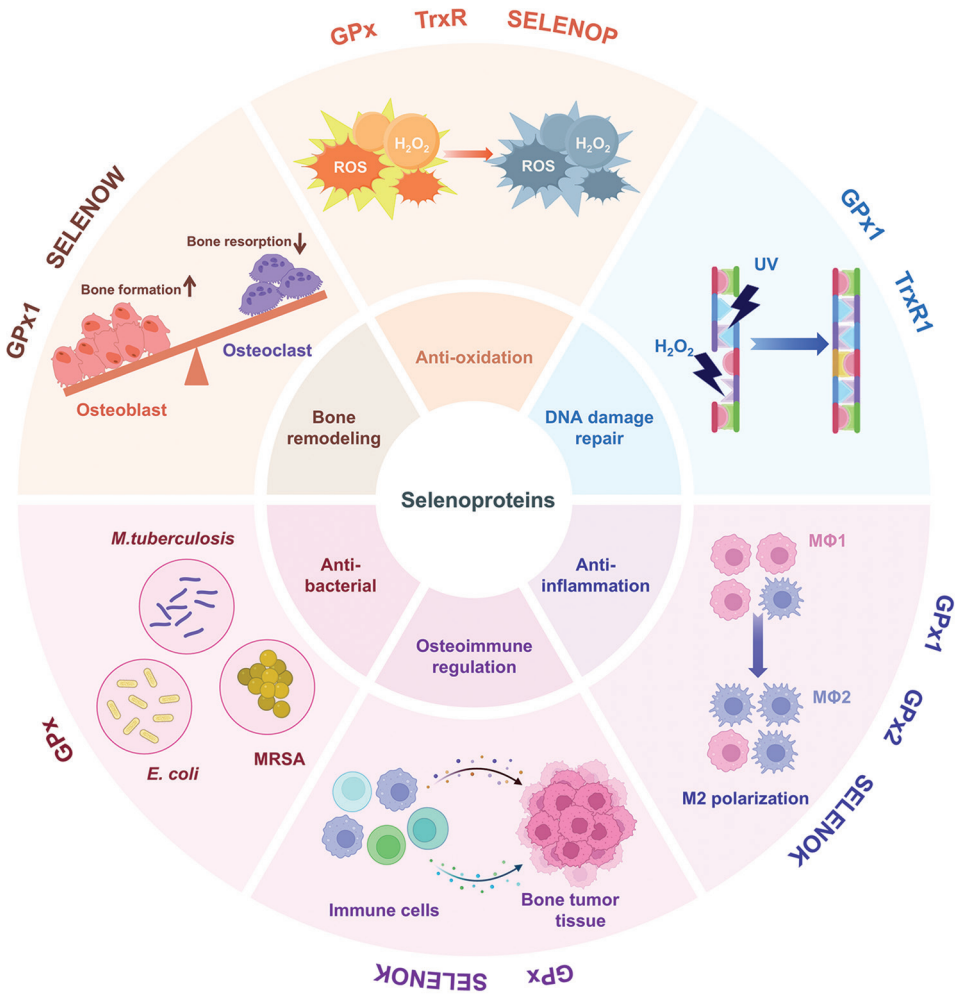

Figure 2. Pathophysiological functions of selenoproteins in bone and joint-related diseases. Created in BioRender. Dongping, L. (2025) https://BioRender.com/c95g624.The agreement number of this figure is AZ280QSXVT.

Abbreviations: *E. coli*, *Escherichia coli;* GPx, Glutathione peroxidase; H_2O_2: Hydrogen peroxide; MRSA: Methicillin-resistant *Staphylococcus aureus*; *M. tuberculosis*: *Mycobacterium tuberculosis*; ROS: Reactive oxygen species; SELENOK: Selenoprotein K; SELENOP: Selenoprotein P; SELENOW: Selenoprotein W; TrxR: Thioredoxin reductase; UV: Ultraviolet.

Table 1. Therapeutic application of selenium-based biomaterials in bone and joint related-diseases

Disease	Material	Target cells	Outcome	Models of disease	References
Bone defects	TSIIA@SeNPs-APS	PC12	Inhibit excessive ROS production, enhance GSH-Px activity, and decrease MDA content	SCI-induced rat model	130
	PCL-μtank scaffolds	hASC	Enhance hASC-mediated bone tissue regeneration	Bilateral 4-mm critically-sized murine calvarial defect model	131
	PDT-TCP-SE	BMSC	Alleviate oxidative damage, inhibit the occurrence of ferroptosis, and promote bone regeneration in osteoporotic bone defect	OP femur defect rat model	132
	PAA/Se-HA	BMSC	Enhance the formation of calcium nodules and bone regeneration at the defect site	New Zealand rabbit femur condylar bone defect model	133
	Se-MBG	RAW 264.7	Enhance bone regeneration and scavenge excessive ROS	Critical-sized skull defect rat model	134
	SF/PCL/HA/Se Janus nanofibrous scaffold	MC3T3-E1	Enhance bone regeneration	Skull defect rat model	135
	M-HAP/PSSG	HOS, MG-63	Form new tibial bone; enhance osteoblast proliferation and osteoblast differentiation	Tibial bone defect rat model	136
	CS-SeNPs	MC3T3-E1	Improve the osteogenic and anti-inflammatory activities of Ti implants	-	137
Osteoporosis	L-Cys@SeNPs	MC3T3-E1	Attenuate Dex-induced osteoporosis and inhibit Dex-induced ROS overproduction	Dex-induced rat OP model	138
	SeNPs	HOS	Overcome bone loss due to estrogen deficiency	Ovariectomized rat model	139
Osteosarcoma	Se-doped TNA	MC3T3-E1, Saos-2	Exhibit anti-tumor effect and suppress the recurrence of osteosarcoma; induce ROS production in osteosarcoma cells and subsequently activate caspase-dependent apoptotic pathways	-	140
	BGS@LDH/Se	Saos-2	Promote bone regeneration, inhibit tumor recurrence, and induce ROS production and tumor cell killing	Calvarial critical-sized defect New Zealand rabbit model	141
	TCP-PLA/GeSe	BMSC	Repair large-segment bone defects and osteosarcoma	Large segment bone defect New Zealand rabbit model	142
	CC/Se-HAp	MNNG/HOS	Induce ROS production and activate the caspase-3 pathway	-	143
Osteoarthritis	OHA/HA-ADH@SeNPs	SW1353	Scavenge ROS and reduce apoptosis	DMM-induced rat OA model	34
	ES NDs	Mouse chondrocyte	Alleviate ferroptosis-induced OA; mitigate oxidative stress-induced ferroptosis; attenuate chondrocyte inflammatory response, suppress cartilage catabolism and promote cartilage anabolism	DMM-induced rat OA model	144
	SeNPs	Mouse chondrocyte	Inhibit IL-1β-induced inflammatory mediator expression, reduce articular cartilage irregularity and knee joint stenosis	DMM-induced rat OA model	145
	Se@Tri-PTs	Caco-2	Resolve arthritis and reduce inflammatory factors	AIA rat model	146
	HA-SeNPs@ AHAMA-HMs	Human primary chondrocyte	Improve oxidative phosphorylation pathway associated with mitochondrial function	DMM-induced rat OA model	147

(Cont'd...)

Table 1. *(Continued)*

Disease	Material	Target cells	Outcome	Models of disease	References
Rheumatoid arthritis	OD-PP®SeNPs	RAW264.7	Scavenge ROS and regulate pH; induce macrophages into M2 polarization to reduce inflammatory cytokines through PI3K/AKT/NF-κB and MAPK pathways	CIA rat model	148
	SeNPs	-	Increase mRNA expression of CAT, GPX1, and COX-2 levels	CFA-induced RA rat model	149
	SeMetFa NPs	-	Target therapy against chronic inflammatory arthritis	CFA-induced RA rat model	150

Abbreviations: AHAMA-HMs: Aldehyde-functionalized hyaluronic acid-based hydrogel microspheres; AIA: Adjuvant-induced arthritis; AKT: Protein kinase B; APS: Astragalus polysaccharides; BGS: Bioactive glass scaffold; BMSCs: Bone marrow stem cells; CAT: Catalase; CC: Catechins; CFA: Complete Freund's adjuvant; CIA: Collagen-induced arthritis; COX-2: Cyclooxygenase-2; CS: Chitosan; Dex: Dexamethasone; DMM: Destabilized medial meniscus; ES NDs: Epigallocatechin-3-gallate-based nanodrugs; GeSe: Germanium selenium; GPx1: Glutathione peroxidase 1; GSH-Px: Glutathione peroxidase; HA: Hydroxyapatite; HAP: Hydroxyapatite; hASC: Human adipose-derived stem cells; HA-ADH: Hyaluronic acid-adipic acid dihydrazide; HOS: Human osteoblast; IL: Interleukin; LDH: Layered double hydroxide; L-Cys: L-cysteine; MAPK: Mitogen-activated protein kinase; MBG: Mesoporous bioactive glass; MDA: Malondialdehyde; MNNG: N-methyl-N'-nitro-N-nitrosoguanidine; mRNA: Messenger RNA; NF-κB: Nuclear factor kappa-B; OA: Osteoarthritis; OD: Oxidised dextran; OHA: Oxidized hyaluronic acid; OP: Osteoporosis; PAA: Poly (amino acid); PCL: Poly-ε-caprolactone; PDT: Poly (lactic acid-carbonate); PI3K: Phosphatidylinositol 3-kinase; PLA: Polylactic acid; PP: Polylysine; PSSG: Poly sorbitol sebacate glutamate; RA: Rheumatoid arthritis; ROS: Reactive oxygen species; SCI: Spinal cord injury; Se: Selenium; SF: Silk fibroin; SeMetFa NPs: Selenium-methionine-folic acid nanoparticles; SeNPs: Selenium nanoparticles; TCP: Tricalcium phosphate; Ti: Titanium; TNA: TiO_2 nanotube array; Tri-PTs: Tripterine phytosomes; TSIIA: Tanshinone IIA.

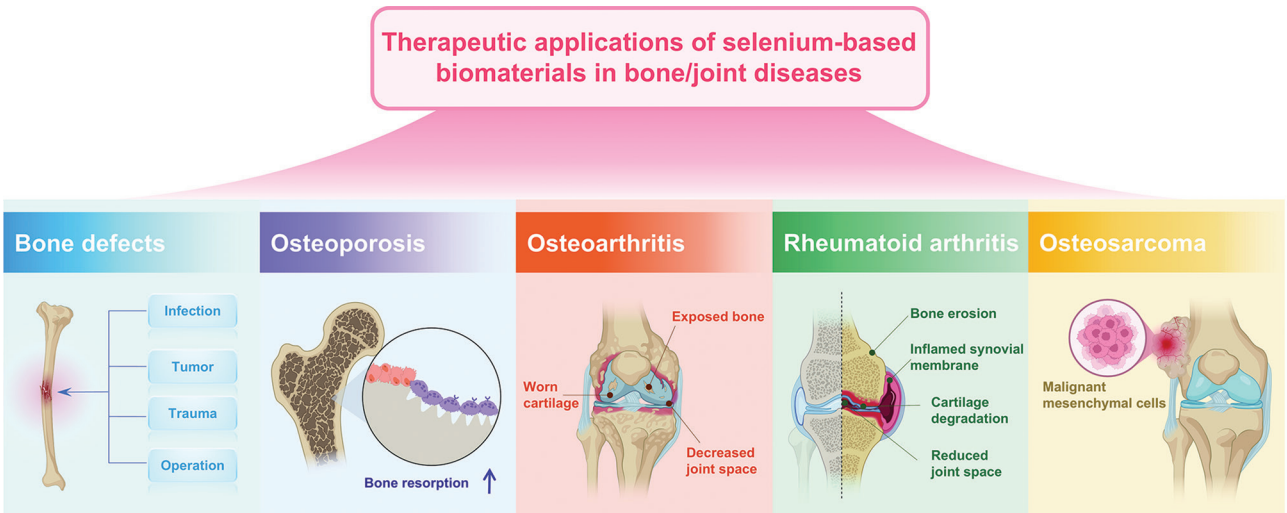

Figure 3. Therapeutic applications of selenium-based biomaterials in bone and joint-related diseases. Created in BioRender. Dongping, L. (2025) https://BioRender.com/l22g186. The agreement number of this figure is FC280QTS0G.

In addition, its corrosion products are not only harmless but also possess anticancer potential and can effectively enhance the corrosion resistance of metal alloys.[151] For instance, Xu *et al.*[137] demonstrated that selenium-doped titanium substrates exhibit enhanced osteogenic and anti-inflammatory properties with minimal cytotoxicity. Tan *et al.*[152] highlighted the protective effects of SeNPs against cobalt nanoparticle-induced toxicity in skeletal muscle, further underscoring their biocompatibility and safety. In addition, He *et al.*[153] showcased the use of ROS-regulated hydrogels containing SeNPs to promote bone regeneration, emphasizing their biocompatibility and therapeutic efficacy. Recent advancements in nanotechnology have opened new avenues for the application of selenium-containing biomaterials. Studies have demonstrated that nano-rough surfaces are more conducive to osteoblast attachment and proliferation,[154] and selenium nano-briquettes outperform traditional selenium metal powders in promoting osteoblast density increase and adhesion.[155] Further research has elucidated the central role of selenoproteins in antioxidant processes and bone damage repair. SeNPs promote stem cell differentiation into osteoblasts by regulating oxidative stress,[156] whereas SELENOW maintains the physiological homeostasis of bone remodeling by inhibiting osteoclast overactivity.[109]

The accumulation of ROS and a hypoxic microenvironment pose significant obstacles to bone regeneration during bone defect repair.[157] While local exogenous selenium supplementation effectively alleviates microenvironmental stress induced by high ROS concentrations, the hypoxic environment caused by ischemia and the reduced activity of BMSCs continue to prolong bone defect healing time.[131] To address this challenge, an innovative hydrogel platform, oxygen-enriched selenium-incorporated thin-shell silicon within methacrylate gelatin (O_2-PSSG), has been proposed. O_2-PSSG nanosystems promote the *in situ* synthesis of intracellular selenoproteins and hydrogen peroxide depletion, thereby mitigating microenvironmental stress caused by high ROS through the ultrasonically modulated release of selenium-containing nanoparticles (**Figure 4Ba** and **b**). Mechanistically,

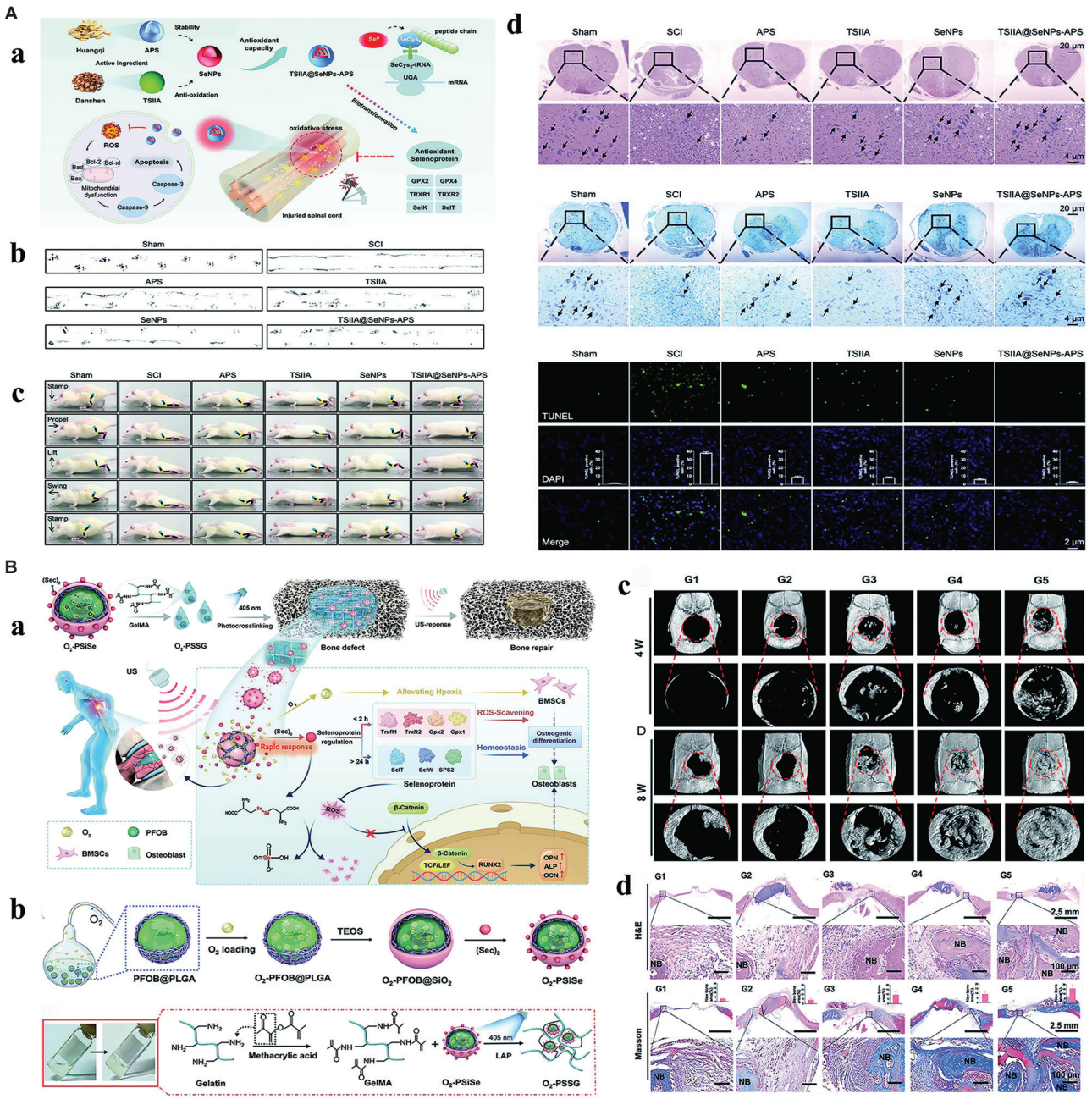

Figure 4. Design and fabrication of selenium-based biomaterials for bone defect treatment. (A) traditional Chinese medicine active ingredient-based SeNPs (TSIIA@SeNPs-APS) for SCI therapy. a. Schematic illustration. b. Footprint analysis of rats. c. Sequence of hindlimb movements in rats. d. Representative images of spinal cord tissues. Reprinted from Rao *et al.*[133] Copyright 2022, Authors. (B) O_2-PSSG for bone defect repair and regeneration. (a) Schematic illustration. (b) Schematic diagram of the synthetic process of the O_2-PSSG hydrogel (c) Micro-computed tomography three-dimensional reconstruction of the skull at 4 and 8 weeks. (d) H&E and Masson's staining of samples from different groups of rats with skull defects at 4 weeks. Reprinted with permission from Xu *et al.*[161] Copyright 2024, Wiley-VCH GmbH.

Abbreviations: ALP: Alkaline phosphatase; APS: Astragalus polysaccharides; Bad: BCL2-associated agonist of cell death; Bax: Bcl-2 Associated X-protein; BMSCs: Bone marrow mesenchymal stem cells; DAPI: 4',6-diamidino-2-phenylindole; GelMA: Gelatin methacryloyl; GPX: Glutathione peroxidase; H&E: Hematoxylin and eosin; LAP: Lithium phenyl-2,4,6-trimethylbenzoylphosphinate; LEF: Lymphoid enhancer-binding factor-1; mRNA: Messenger RNA; NB: New bone; OCN: Osteocalcin; OPN: Osteopontin; O_2: Oxygen; O_2-PSSG: Oxygen-enriched selene-incorporated thin-shell silicon within methacrylate gelatin; PFOB: Perfluorooctyl bromide; PLGA: Poly lactic-co-glycolic acid; PsiSe: Selenide thin-shell silicon nanosystem; ROS: Reactive oxygen species; RUNX2: Runt-related transcription factor 2; SCI: Spinal cord injury; $SeCys_2$: Selenocysteine; SelK: Selenoprotein K; SelT: Selenoprotein T; SelW: Selenoprotein W; SeNPs: Selenium nanoparticles; SiO_2: Silicon dioxide; SPS2: Selenophosphate synthetase 2; TCF: T cell factor; TEOS: Tetraethyl silicate; tRNA: Transfer RNA; TRXR: Thioredoxin reductase; TSIIA: Tanshinone IIA; TUNEL: Terminal nucleotidyl transferase-mediated dUTP-biotin nick end-labeling; US: Ultrasound; $(Sec)_2$: Selenocystine.

O_2-PSSG nanosystems activate the osteogenic differentiation of BMSCs via the nuclear translocation of the key transcription factor β-catenin. In a rat model of critical cranial defects, O_2-PSSG demonstrated significant bone repair effects under

ultrasound modulation (**Figure 4Bc**).[158] To further address the issue of bacterial infection associated with implant materials, researchers have developed novel scaffold materials that integrate antibacterial and pro-tissue regeneration properties. Three-dimensional (3D)-printed scaffolds coated with SeNPs and calcium phosphate effectively inhibit key pathogens such as *S. aureus* through various mechanisms, including ROS generation and disruption of bacterial cell membranes and DNA. These scaffolds also exhibit excellent bone-enhancing properties, offering a promising therapeutic strategy for bone defect repair.[97]

In addition, researchers synthesized hydroxyapatite nanoparticles through aqueous co-precipitation and subsequently doped them with selenium trace elements to create selenium-doped hydroxyapatite nanoparticle (Se-HAN) biocomposites. This material exhibited favorable osteogenic potential, biocompatibility, and biodegradability, and its manufacturing process was relatively simple, making it a promising candidate for bone defect repair.[159, 160] Se-HANs were found to induce tumor cell apoptosis through a cystatinase-dependent apoptotic pathway synergistically coordinated with the production of ROS.[161] These nanoparticles have the potential to fill bone defects resulting from bone tumor resection while simultaneously eliminating residual tumor cells. *In vivo,* animal studies further confirmed that 10% Se-HANs significantly induced tumor apoptosis, inhibited tumor growth, and reduced systemic toxicity.[159] Building upon these findings, it can be inferred that Se-HAN biocomposites significantly enhance bone defect repair as bioactive bone graft substitutes.

4.2. Osteoporosis

Osteoporosis is a common skeletal disorder characterized by decreased bone mineral density and an increased risk of fracture.[162, 163] Diabetic osteoporosis is a highly prevalent and severely harmful complication. A meta-analysis indicated a 32% greater incidence of fractures in diabetic patients compared to non-diabetic individuals.[164] Moreover, hyperglycemic conditions significantly impair bone remodeling and regeneration in diabetics, delaying bone injury healing.[165] SeNPs have demonstrated the ability to activate the bone morphogenetic protein 2/MAPK/β-catenin signaling pathway, enhancing osteogenesis under hyperglycemic conditions by inducing Runt-related transcription factor 2 expression. Simultaneously, these nanoparticles reduce ROS levels.[33]

Recently, Xiong *et al.*[138] skillfully designed and constructed cysteine-modified chiral SeNPs (Cys@SeNPs) (**Figure 5Aa** and **b**). Compared to D-Cys@SeNP and DL-Cys@SeNPs, L-Cys@SeNPs were smaller and more negatively charged. The chiral design of L-Cys@SeNPs enhanced their interaction with cellular receptors, leading to improved internalization and bioavailability in osteoblasts compared to D-Cys@SeNPs. Intracellular L-Cys@SeNPs were primarily converted into Sec, which upregulated the production of antioxidative selenoproteins, effectively scavenging dexamethasone (Dex)-induced excessive ROS accumulation in osteoblasts. This process minimized detrimental apoptosis through activation of the Wnt/β-catenin pathway. Furthermore, L-Cys@SeNPs significantly alleviated osteoporosis symptoms *in vivo*, characterized by the reduction in trabecular bone destruction and the restoration of bone mineral density (**Figure 5Ac**). They also reduced body weight gain and fatty liver formation in Dex-exposed mice, therefore mitigating the overall negative effects of Dex (**Figure 5Ad**). The chiral specificity of L-Cys@SeNPs not only enhanced their cellular uptake but also modulated downstream osteogenic signaling pathways, such as Wnt/β-catenin, which are crucial for bone formation and osteoporosis treatment.

In addition to osteoporosis resulting from underlying medical conditions, the adverse effects of pharmacological treatments also contribute significantly to the progression of the disease. Aromatase inhibitors such as anastrozole play a crucial role in breast cancer treatment, but their chronic use can lead to a significant decrease in bone density and an increased risk of osteoporosis.[166] However, studies have demonstrated that SeNPs can prevent this bone loss in a dose-dependent manner.[139] When administered alongside anastrozole, SeNPs mitigate the bone toxicity induced by the drug, reducing the potential bone damage. In a female Sprague-Dawley rat model, SeNPs (0.25, 0.5, and 1 mg/kg/day) effectively countered the anastrozole-induced (0.2 mg/kg/day) reduction in bone density and elevation of bone resorption biomarkers. Overall, these findings suggest that SeNPs exhibit effective therapeutic potential for osteoporosis treatment.

Selenium-modified bioactive materials have also emerged as a promising approach for osteoporosis treatment. For instance, Zhou *et al.*[75] fabricated a selenium-modified bioactive silk fibroin and calcium phosphate cement scaffold (**Figure 5Ba**). After 8 weeks of implantation in OVX rats, new bone tissue formation and enhanced GPx1 expression were observed (**Figure 5Bb** and **c**). These results suggest that selenium supplementation accelerates the regeneration of osteoporotic bone defects in OVX rats by activating the GPx1-mediated antioxidant pathway.

4.3. Osteosarcoma (OS)

OS, a primary malignant solid tumor primarily affecting children and adolescents, originates from osteogenic stem cells and predominantly manifests in the distal femur and proximal tibia.[167-169] The primary treatment modalities for OS include surgical resection, chemotherapy, and radiotherapy.[170, 171] Despite its sensitivity to chemotherapy, OS frequently metastasizes to the lungs, leading to high morbidity and mortality rates. Radical resection remains the primary therapeutic option, necessitating bone repair to alleviate physical impairments.[140, 172] Given that post-surgical bone defects often exceed the body's natural healing capacity, osteogenic biomaterials are essential. Therefore, there is an urgent need for a multifunctional artificial bone substitute that can effectively eliminate residual tumor cells to prevent recurrence while also possessing remarkable bone reconstruction capacity.

As post-surgical bone defects often surpass the body's self-healing capabilities, osteogenic biomaterials are indispensable. For example, Bian *et al.*[141] synthesized

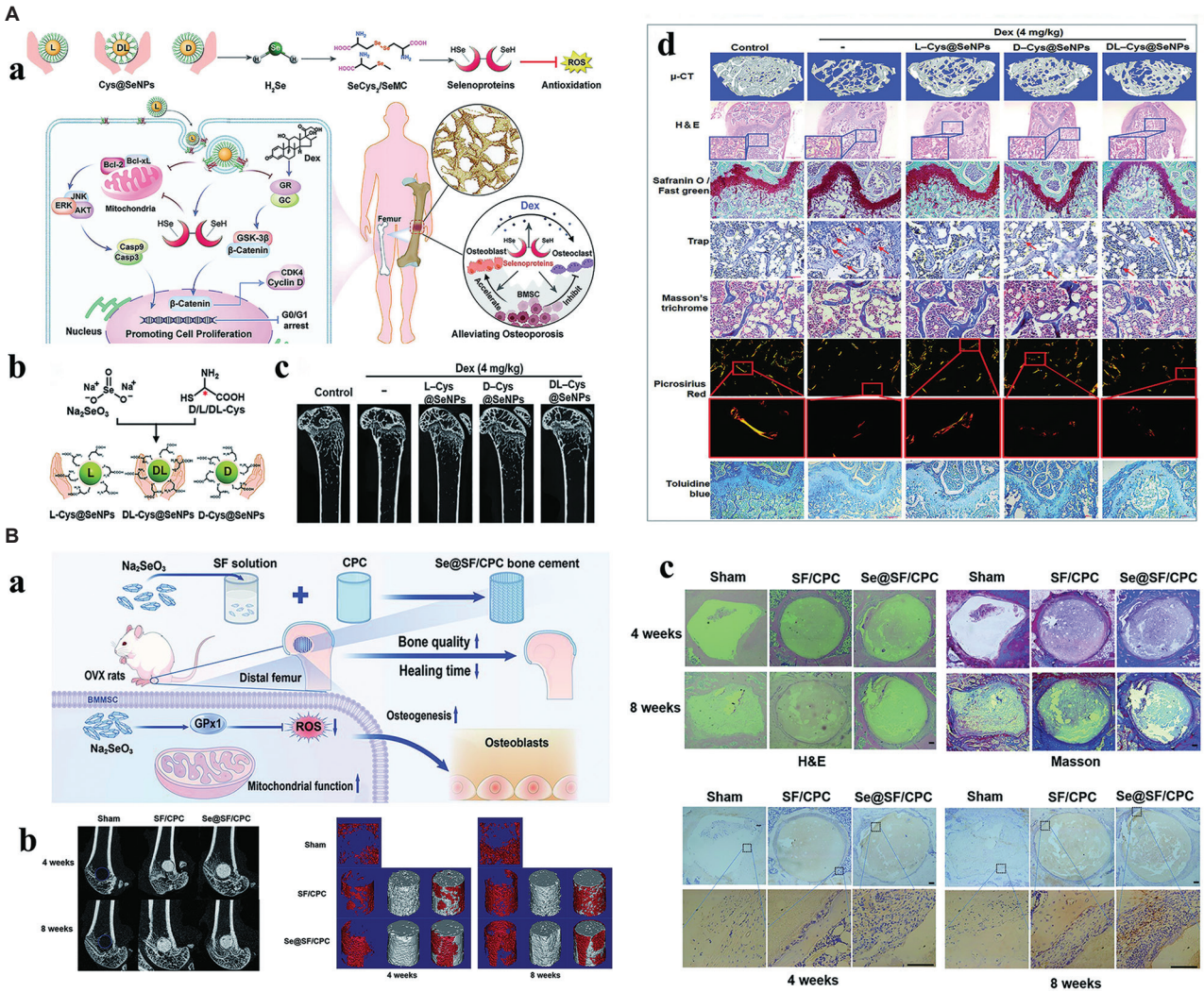

Figure 5. Design and fabrication of selenium-based biomaterials for osteoporosis therapy. (A) Chiral selenium nanomedicine of Cys@SeNPs for the treatment of glucocorticoid-induced osteoporosis. (a) Schematic illustration. (b) Schematic depiction of the fabrication of Cys@SeNPs. (c) μ-CT images show the microstructures in femurs. d. Immunohistochemical analysis of bone tissue. Reprinted with permission from Xiong *et al.*[141] Copyright 2023, Wiley-VCH GmbH. (B) SF/CPC for treating osteoporotic bone fractures. (a) Schematic illustration. (b) Images from micro-CT analysis. (c) Histological and immunohistochemical images. Reprinted from Zhou *et al.*[75] Copyright 2023, Authors.
Abbreviations: AKT: Protein kinase B; Bcl-XL: B-cell lymphoma-extra large; Bcl-2: B-cell lymphoma 2; BMSC: Bone marrow stem cell; CDK4: cyclin-dependent kinase 4; CPC: Calcium phosphate cement; CT: Computed tomography; Cys: Cysteine; Dex: Dexamethasone; ERK: Extracellular signal-regulated kinase; GC: Vitamin-D binding protein; Gpx1: Glutathione peroxidase 1; GR: Glucocorticoid receptor; GSK-3β: Glycogen synthase kinase 3 beta; H&E: Hematoxylin and eosin; JNK: c-Jun N-terminal kinase; OVX: Ovariectomised; ROS: Reactive oxygen species; Se: Selenium; SeMC: Selenium-methylselenocysteine; SeNPs: Selenium nanoparticles; $SeCys_2$: Selenocysteine; SF: Silk fibroin.

magnesium ferrum-layered double hydroxide (LDH) using a co-precipitation approach, followed by the "*in-situ* reduction method" to produce SeNPs-incorporated LDH nanocomposite (LDH/Se). The LDH/Se was subsequently loaded onto a 3D-printed bioactive glass scaffold, creating a multifunctional platform for OS eradication with antibacterial properties and the ability to support bone reconstruction (**Figure 6Aa**). The LDH/Se ensured uniform dispersion of negatively charged SeNPs on the LDH surface, thereby minimizing aggregation and inactivation, which could otherwise induce toxicity. This enhanced the activation of superoxide dismutase and facilitated the conversion of superoxide anion radical to H_2O_2 (**Figure 6Ab** and **c**). Xu *et al.*[142] adopted a different approach by designing a selenium-based biomimetic scaffold that integrates piezoelectric properties with photothermal conversion capabilities (**Figure 6Ba**). They used electrospinning technology to develop a germanium selenium (GeSe)-co-doped polylactic acid (PLA) nanofiber membrane-coated tricalcium phosphate (TCP) bioceramic scaffold, resulting in the TCP-PLA/GeSe scaffold. This innovative biomimetic scaffold exhibited dual functionalities, combining piezoelectric properties with photothermal conversion capabilities while maintaining biodegradability. In rabbit models with large bone defects, the TCP-PLA/GeSe scaffold enhanced bone formation and promoted the inward growth of nerve fibers (**Figure 6Bb**). Furthermore, its high photothermal conversion and sustained antitumor selenium release synergistically counteracted OS both *in vitro* and *in vivo*. Selenium stimulated the production of hydroxyl radicals in cells, accelerating cell death and enhancing tumor treatment efficacy (**Figure 6Bc**). In a subcutaneous

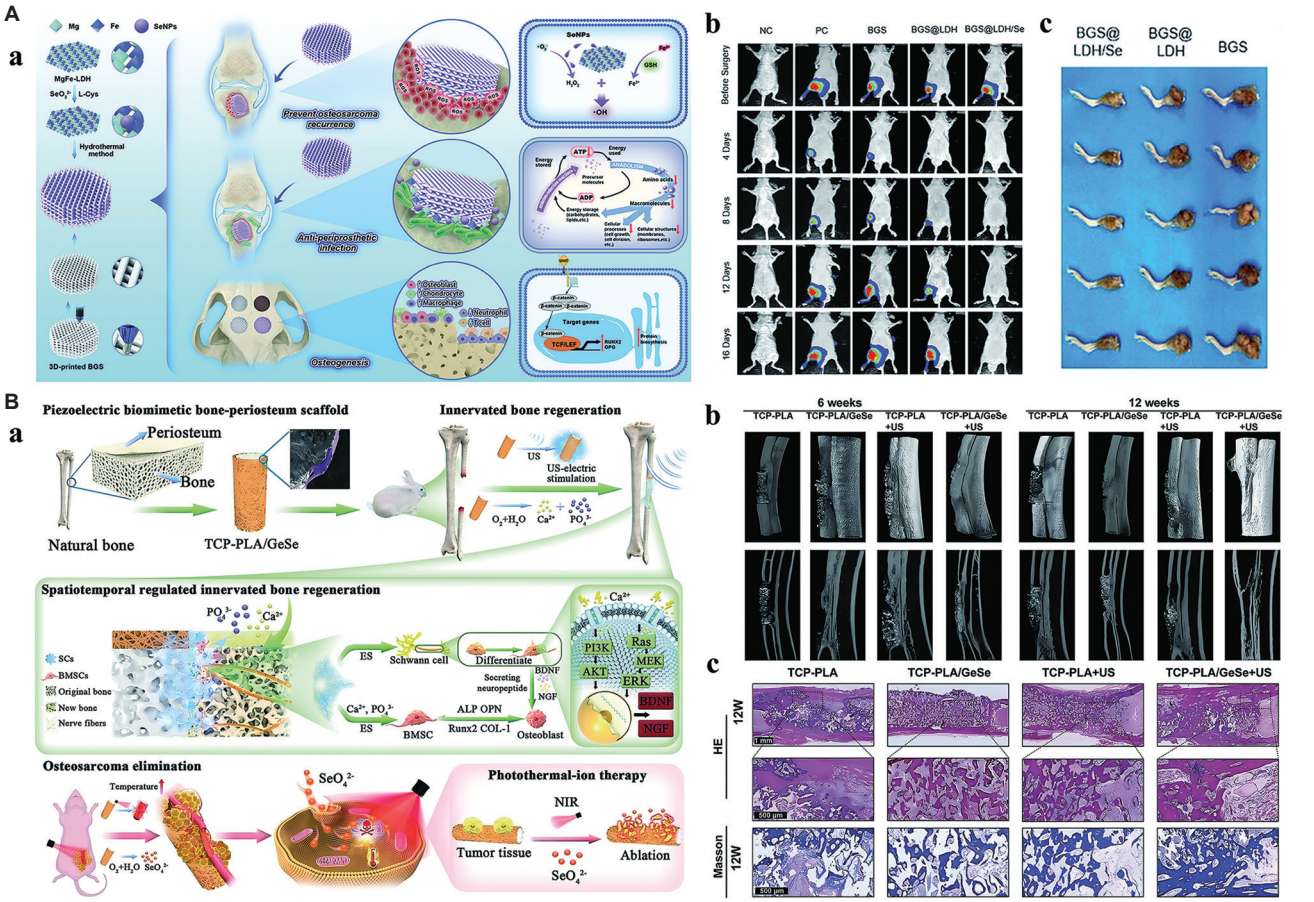

Figure 6. Design and fabrication of selenium-based biomaterials for multimodal osteosarcoma therapy. (A) A multifunctional SeNPs-incorporated MgFe-LDH nanosheet platform for osteosarcoma treatment. (a) Schematic illustration. (b) Bioluminescence monitoring of tumor activity. (c) Gross images of the knee and surrounding tissues of mice in different treatment groups. Reprinted from Bian *et al.*[144] Copyright 2024, Authors. (B) A piezoelectric biomimetic bone-periosteum scaffold (TCP-PLA/GeSe) for osteosarcoma treatment. (a) Schematic illustration. (b) 3D-reconstructed images of newly formed bones. c. Photographs of bone regeneration tissue. Reprinted from Xu *et al.*[145] Copyright 2024, Authors.

Abbreviations: ADP: Adenosine diphosphate; AKT: Protein kinase B; ALP: Alkaline phosphatase; ATP: Adenosine triphosphate; BDNF: Brain-derived neurotrophic factor; BGS: Bioactive glass scaffold; BMSCs: Bone marrow stem cells; Ca^{2+}: Calcium ion; COL-1: Type 1 collagen; Cys: Cysteine; ERK: Extracellular signal-regulated kinase; ES: Emission spectrometer Fe: Ferrum; GeSe: Germanium selenium; GSH: Glutathione; HE: Hematoxylin and eosin; H_2O: Water; H_2O_2: Hydrogen peroxide; LDH: Layered double hydroxide; LEF: Lymphoid enhancer-binding factor-1; MEK: Mitogen-activated protein kinase; Mg: Magnesium; NC: Negative control group; NGF: Nerve growth factor; NIR: Near-infrared; OPG: Ostoeprotegerin; OPN: Osteopontin; PC: Positive control group; PI3K: Phosphatidylinositol 3-kinase; PO_4^{3-}: Phosphate ion; O_2: Oxygen; PLA: Polylactic acid; Ras: Rat sarcoma virus protein; RUNX2: Runt-related transcription factor 2; SCs: Schwann cells; SeNPs: Selenium nanoparticles; SeO_3^{2-}: Selenite; SeO_4^{2-}: Selenate; TCF: T cell factor; TCP: Tricalcium phosphate; US: Ultrasound; 3D: Three-dimension; -OH: hydroxyl radicals; $\cdot O_2^-$: Superoxide anion radical.

tumor model, the combination of local photothermal ablation and the antitumor effect of selenium effectively eradicated the tumors. Xu *et al.*[173] integrated iron phosphorus triselenide ($FePSe_3$) nanosheets onto 3D-printed α-TCP scaffolds to create a bifunctional TCP-$FePSe_3$ scaffold for synergistic OS treatment. This scaffold exhibited photothermal properties that rapidly eliminated tumor cells under near-infrared irradiation. At the same time, its rapid degradation released selenium, which inhibited tumor recurrence by activating caspase-dependent apoptosis pathways.

In addition, selenium nanocomposites represent a prevalent therapeutic approach for OS treatment. Khan *et al.*[143] developed catechin-modified selenium-doped hydroxyapatite nanocomposites for potential OS therapy. Tran *et al.*[174] combined the anticancer activity of SeNPs with the mechanical properties of titanium to create a novel anticancer bone implant. SeNPs promoted normal osteoblast proliferation while inhibiting cancerous osteoblast growth in both monoculture and coculture experiments. The use of SeNPs in anticancer orthopedic implants was rationalized by the fact that corrosion products of selenium may directly act as anticancer agents or be utilized by surrounding tissues to prevent cancer or recurrence.[139]

4.4. OA

OA is the most common degenerative joint disease and a leading cause of chronic pain and disability in the elderly.[175] Characterized by the progressive degeneration of articular

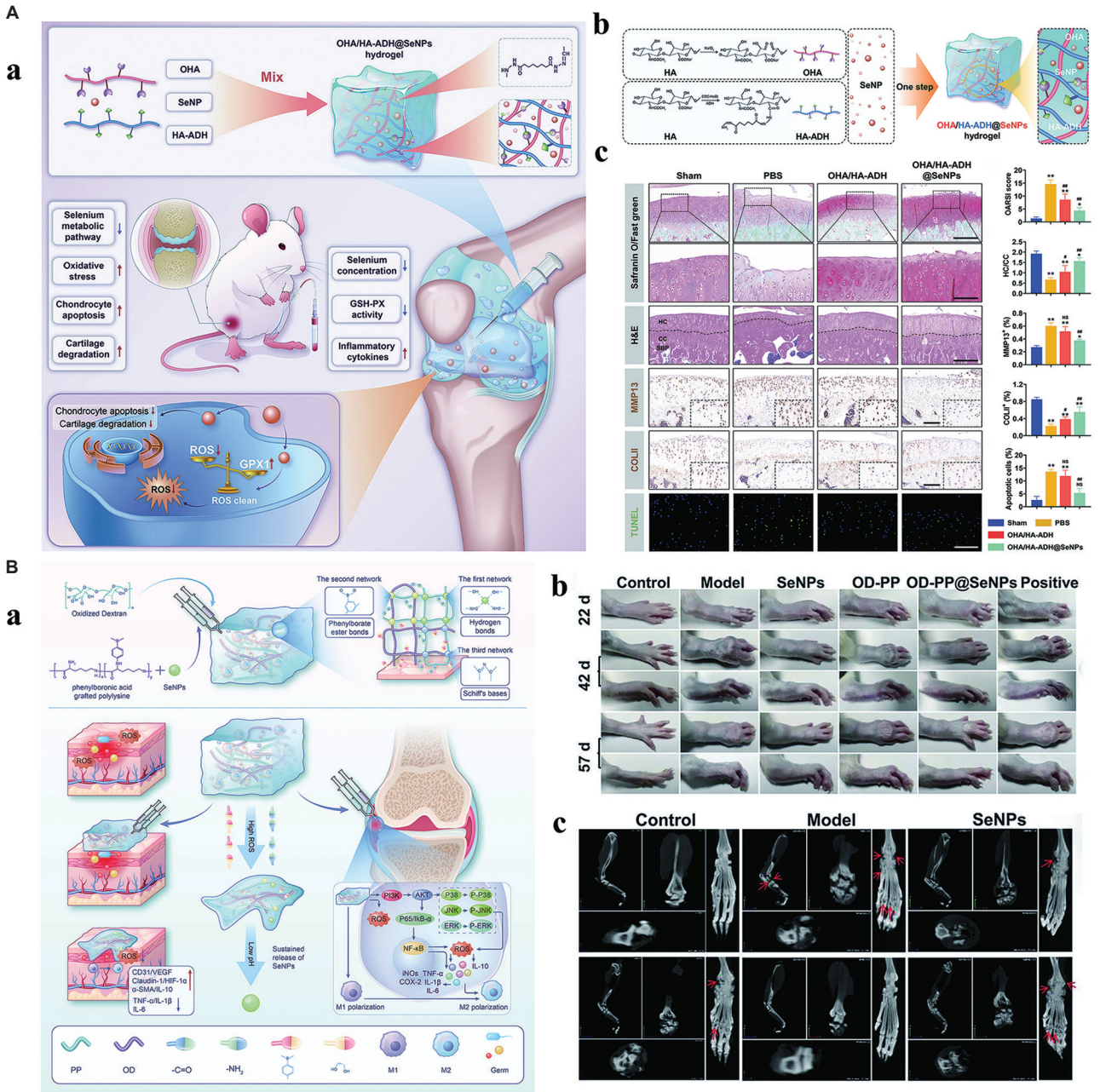

Figure 7. Design and fabrication of selenium-based biomaterials for the treatment of osteoarthritis and rheumatoid arthritis. (A) OHA/HA-ADH@SeNPs hydrogels addressing selenium imbalance in biomaterial development for osteoarthritis. (a) Schematic illustration. (b) Schematic diagram of the synthesis of OHA/HA-ADH@SeNPs hydrogel. (c) Evaluation of cartilage repair *in vivo*. Reprinted from Hu *et al.*[34] Copyright 2023, Authors. (B) An inflammatory microenvironment-responsive hydrogel (OD-PP@SeNPs) for rheumatoid arthritis treatment. (a) Schematic illustration. (b) Hind paw images of rheumatoid arthritis rats in different groups. (c) Paw X-ray images of rheumatoid arthritis rats with detailed ankle images for each group. Reprinted from Wang *et al.*[151] Copyright 2023, Authors.

Abbreviations: ADH: Adipic dihydrazide; Akt: Protein kinase B; CD31: Cluster of differentiation 31; COLII, type II collagen; COX-2: Cyclooxygenase-2; ERK: Extracellular signal-regulated kinase; GPX1: Glutathione peroxidase 1; HA: Hyaluronic acid; HIF-1α: Hypoxia-inducible factor-1α; H&E: Hematoxylin and eosin; IL-10: Interleukin-10; IL-1β: Interleukin-1β; IL-6: Interleukin-6; iNOs: Inducible nitric oxide synthase; JNK: c-Jun N-terminal kinase; NF-κB: Nuclear factor kappa-B; MMP13: Matrix metalloproteinase-13; OD: Oxidized dextran; OHA: Oxidized hyaluronic acid; PI3K: Phosphatidylinositol 3-kinase; PP: Phenylboronic acid grafted polylysine; ROS: Reactive oxygen species; SeNP: Selenium nanoparticle; TNF-α: Tumor necrosis factor alpha; TUNEL: Terminal nucleotidyl transferase-mediated dUTP-biotin nick end-labeling; VEGF: Vascular endothelial growth factor; α-SMA: Alpha-smooth muscle actin.

cartilage, OA often requires joint replacement surgery in end-stage cases with severe cartilage destruction.[176] However, post-operative joint dysfunction and the limited lifespan of replacement joints may necessitate reoperation, leading to additional costs and pain.[175] Encapsulating SeNPs in hydrogels offers controlled and sustained release, ensuring prolonged therapeutic effects while minimizing toxicity risks. Hydrogels also provide mechanical protection, biocompatibility, and

stimuli-responsive targeting, making them highly effective for OA treatment.[177,178] A novel injectable hydrogel for sustained selenoprotein modulation and OA therapy has been introduced (**Figure 7Aa**).[34] This hydrogel is conveniently fabricated through a one-step mixing process involving oxidized hyaluronic acid (OHA), adipic dihydrazide-grafted hyaluronic acid (HA-ADH), and SeNPs. The mild Schiff base reaction between OHA and HA-ADH, coupled with SeNP dispersion within the gel network, enables the formation of the OHA/HA-ADH@SeNPs hydrogel (**Figure 7Ab**). Hydrogels encapsulating SeNPs promote cartilage repair by targeting selenoprotein GPx1 and inhibiting cell apoptosis. *In vivo* studies using a destabilized medial meniscus rat model demonstrated that the OHA/HA-ADH@SeNPs hydrogel significantly ameliorated OA symptoms (**Figure 7Ac**). Liu *et al.*[147] designed a cascade-targeted delivery system, which first prepared hydrogel microspheres AHAMA-HMs using aldehyde-modified methacrylated hyaluronic acid (AHAMA), and then loaded hyaluronic acid-modified nano-selenium (HA-SeNPs) into them through a nano-microcomposite strategy. AHAMA-HMs adhere to the damaged cartilage surface through the Schiff base reaction to achieve micron-level targeting, while HA-SeNPs can target the nanoscale by binding to CD44 receptors, which are highly expressed on the OA chondrocyte membrane. Yu *et al.*[144] efficiently synthesized epigallocatechin-3-gallate (EGCG)-based nanodrugs (ES NDs) for OA treatment in an aqueous medium using the Mannich condensation reaction between the antioxidant SeMet and EGCG. ES NDs effectively inhibit ferroptosis by reducing GPx4 inactivation, abnormal Fe^{2+} accumulation, and lipid peroxidation, thereby restoring chondrocyte metabolism and alleviating oxidative stress-induced damage. Previous research has shown that SeMet supplementation enhances GPx4 expression at the cellular level and effectively mitigates lipid ROS production.[179] The findings suggest that ES NDs effectively counteract GPx4 inactivation due to oxidative stress, improving chondrocyte metabolic disorders. Furthermore, *in vitro* and *in vivo* studies by Li *et al.*[145] confirmed that SeNPs alleviate OA-associated pain by suppressing ROS production in IL-1β-stimulated cells and enhancing GPx activity, which in turn inhibits the NF-κB p65 and p38/MAPK signaling pathways. Selenium-deposited tripterine phytosomes (Se@Tri-PTs) were prepared using a melting-hydration/*in situ* reduction technique.[146] Phytosomes facilitated the transepithelial transport of tripterine, while selenium enhanced the anti-arthritic efficacy of the phytomedicine synergistically. *In vivo,* anti-arthritic tests demonstrated that Se@Tri-PTs significantly resolved arthritis and reduced inflammatory factors. Compared to Tri-PTs, Se@Tri-PTs exhibited a superior *in vivo* anti-inflammatory effect. These findings suggest a novel approach for formulating anti-inflammatory phytomedicines and selenium into a two-in-one nanomedicine for treating inflammatory diseases.

4.5. RA

RA is a chronic autoimmune disease characterized by synovial hyperplasia, which leads to bone and cartilage degradation.[180, 181] Treatment options for RA patients encompass non-steroidal anti-inflammatory drugs, glucocorticoids, and disease-modifying antirheumatic drugs. However, these therapies are often constrained by significant adverse effects, including cardiovascular disease, hepatic and renal damage, and intestinal ulceration.[182] In this context, the use of multifunctional nanoparticles has emerged as a promising approach to enhance RA treatment efficacy while mitigating dose-related side effects.[183, 184]

SeNPs are a promising therapeutic option for RA patients due to their potent antioxidant and anti-inflammatory properties. Liu *et al.* designed and synthesized peptide-assembled SeNPs (Se@RuNPs), which exhibited notable therapeutic effects in RA by significantly reducing synovitis, cartilage erosion, and inflammatory cytokine expression.[180] These nanoparticles stimulate NO production through iNOS induction, inhibiting local neovascularization. Furthermore, NO enhances adenosine monophosphate-activated protein kinase phosphorylation and suppresses the mammalian target of rapamycin phosphorylation, promoting autophagic flux. Furthermore, Wang *et al.*[148] prepared a dynamically responsive hydrogel with a triple-network structure, oxidized dextran (OD)-phenylboronic acid grafted polylysine (PP)@SeNPs. This composite hydrogel induced macrophages to polarize to the M2 phenotype, reduced inflammatory cytokines through the PI3K/AKT/NF-κB and MAPK pathways, exerted anti-inflammatory effects, and facilitated the remodeling of the inflammatory microenvironment (**Figure 7Ba**). In a collagen-induced arthritis rat model, OD-PP@SeNPs hydrogel inhibited synovial hyperplasia and inflammation, reduced osteoclast formation, improved cartilage and bone remodeling, alleviated paw swelling in collagen-induced arthritis rats, and achieved therapeutic effects in relieving RA (**Figure 7Bb** and **c**).

Ren *et al.*[149] recently demonstrated that SeNPs dispersed in a specific phytochemical significantly reduced inflammation in an RA rat model by modulating catalase, GPx1, and cyclooxygenase-2 gene expression. Similarly, Arif *et al.*[185] treated RA using *Foeniculum vulgare* Mill.-derived SeNPs. In summary, targeted therapy using multifunctional SeNPs (such as Se@RuNPs [ruthenium nanoparticles] and OD-PP@SeNPs) not only enhances the therapeutic efficacy of RA but also significantly reduces drug-related side effects.

5. Conclusions

Numerous studies have demonstrated a strong correlation between selenium metabolism and the development of bone and joint-related diseases. Selenium plays a significant role in the pathophysiology of these diseases through mechanisms such as oxidative stress and immune response. Adequate selenium supplementation has been shown to prevent and treat bone and joint disorders. However, the specific functions of certain selenoproteins, including GPx6 and selenoprotein V, remain unclear. A deeper understanding of how selenoproteins regulate bone and cartilage homeostasis is necessary. Over the years, researchers have investigated a wide range of natural and synthetic selenium compounds with potential therapeutic applications for bone and joint-related diseases. Recent advancements in nanotechnology have significantly enhanced the functional study of SeNPs. Through modifications, SeNPs have become not only more

bioavailable than organic selenium compounds but also less toxic than inorganic selenium compounds. Despite their promise, challenges such as precise dose control, long-term biocompatibility, and scalable production need to be addressed for the clinical translation of selenium-based biomaterials.[186-188] Future research should focus on optimizing selenium delivery systems, conducting multicenter clinical trials, and fostering industry collaboration to overcome these barriers.[189] With continued research and development, it is expected that more selenium-supplemented formulations and products will be utilized in the treatment of bone and joint-related diseases. Selenium supplementation could thus become an adjunctive therapy for clinical application in these conditions.

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The authors declare no conflicts of interest.
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Ethics approval and consent to participate
Not applicable.
Consent for publication
Not applicable.
Availability of data
Not applicable.
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