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REVIEW

Repair mechanisms of bone system tissues based on comprehensive perspective of multi-omics

Honghao Yu · Shize Yang · Tianlong Jiang · Tian Li · Hongmei Duan · Minglei Li

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Abstract Bone disorders affect more than half of the adult population worldwide who may have a poor quality of life and physical independence worldwide. Multi-omic techniques are increasingly adopted and applied to determine the molecular mechanisms of bone tissue repair, providing perspective towards personalized medical intervention. Data from genomics, epigenomics, transcriptomics, proteomics, glycomics, and lipidomics were combined to elucidate dynamic processes in bone repair. In this narrative review, the key role of genetic and epigenetic factors in regulating injured cellular responses is highlighted, and changes in RNA and protein expression during the healing phase, as well as glucolipid metabolism adaptation, are described in detail how the repair process is affected. In a word, the integration of multi-omic techniques in this review not only benefits the comprehensive identification of new biomarkers, but also facilitates the development of personalized treatment strategies of bone disorders to revolutionize regenerative medicine.

Keywords Bone repair · Personalized treatment · Multiomics · Biomarker

Honghao Yu, Tianlong Jiang, Shize Yang contributed equal in this review.

H. Yu
Departments of Spine Surgery, Shengjing Hospital of China Medical University, Shengyang, China

S. Yang
Department of Thoracic Surgery, First Affiliated Hospital of China Medical University, Shenyang 110001, China

T. Jiang
Department of Orthopedic Surgery, First Affiliated Hospital of China Medical University, Shenyang 110001, China

T. Li (✉)
Tianjin Key Laboratory of Acute Abdomen Disease-Associated Organ Injury and ITCWM Repair, Institute of Integrative Medicine of Acute Abdominal Diseases, Tianjin Nankai Hospital, Tianjin Medical University, 8 Changjiang Avenue, Tianjin 300100, China
e-mail: fmmult@foxmail.com; tli@tmu.edu.cn

H. Duan (✉)
Department of Rheumatology and Immunology, First Affiliated Hospital of China Medical University, Shenyang 110001, China
e-mail: melody_dl@sina.com

M. Li (✉)
Department of Pediatric Orthopaedics, Shengjing Hospital of China Medical University, 36 Sanhao St, Shenyang 110004, China
e-mail: mingleibrian@163.com

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Introduction

Cartilage, bone, ligaments, and muscle, all of which make up the musculoskeletal system, are crucial for physical activity and independent living (Wixted et al. 2018). Musculoskeletal disorders remain main chronic disease worldwide (Wang et al. 2023, Wei et al. 2022, Gao et al. 2021, Gao et al. 2022). The International Classification of Diseases (ICD) describes musculoskeletal disorders as conditions concerning the musculoskeletal system or related metabolic immune diseases (Yu et al. 2023). Yet half of all people older than 18 years suffer from musculoskeletal disorders (Yelin et al. 2016), and there are significant differences in their ability to heal trauma (Magarò et al. 2021). Bone injury is a common serious form among musculoskeletal disorders, mainly resulting from osteoporosis, arthritis, bone tumors, and fracture, which are often accompanied by severe pain and affect mobility (Wang et al. 2022). Bone healing takes place as a reaction to an injury (Martin et al. 2019). Exosome delivery, gene therapy, and small molecule regulation are among the cell-free approaches recently recommended for bone tissue engineering (Yang et al. 2023). However, there is still a considerable challenge in managing bone defects caused by skeletal injuries or bone diseases. To date, the increased bone injuries and the limitations of clinical solutions have hinted at the need for finding molecular mechanisms tailored to bone tissue injury for precision therapy in bone healing.

Multi-omics is multi-level and multi-hierarchical and refers to the analysis of multiple data from different groups of genomes, transcriptomes, proteomes, epigenomes, lipidomics, glycomics, and other groups, as well as the synthesis of the resultant data (Baysoy et al. 2023, Akhoundova and Rubin 2022). Genomics, which investigates structure, function, evolution, mapping, and editing of genomes. Epigenomics, on the other hand, focuses on the characterization of reversible modifications of DNA or DNA-associated proteins. Transcriptomics shifts from DNA to RNA, focusing on the RNA transcripts produced by the genome in a particular situation or in a particular cell, while proteomics studies the complete set of proteins actually produced by the cell/organism. Additionally, lipidomics and glycomics are the comprehensive analysis of metabolites in biological specimens.

This review aims to comprehensively summarize the contribution of gene expression profiles, epigenomic modification, energy requirements and lipid signaling of osteoblast for bone tissue repair in the musculoskeletal system based on multi-omics information. Research findings ranging from the role of genetic and epigenetic factors in mediating cellular responses to injury, to detailed mapping of RNA and protein expression during healing, to glucolipid metabolism adaptations occurring within the restored tissue are integrated. In addition, biomarkers in bone repair and regeneration are explored through the development of computational models and the integration of machine learning techniques, paving the scientific way for personalized therapeutic approaches in regenerative medicine (Table 1).

Searching methods

The search strategy was in accordance with previous literature (Li et al. 2021, Chen et al. 2023, Li et al. 2022, Ning et al. 2022) with minor revision. A comprehensive search was conducted across the databases MEDLINE, EMBASE, BIOSIS, and Cochrane Library, utilizing related terms from inception to Dec 2024. For all databases, controlled or curated vocabulary was employed. However, an additional

Table 1 The main function of potantial miRNAs and lncRNAs in promoting bone repair

name	Mechanisms	Ref
miR-126	enhance the expression of angiogenesis-related genes	(Jia et al. 2019)
miR-29a	facilitate matrix mineralization and increase the expression of osteogenic markers	(Roberto et al. 2014)
miR-451	enhance mineralization both in vitro and in vivo by suppressing Odd Skipped Related 1 while promoting the expression of RUNX2 and BMP-4	(Karvande et al. 2018)
miR-503	facilitate both osteogenic differentiation and mineralization by targeting SMURF1	(Sun et al. 2017)
miR-223-3p	promote osteogenic marker levels and even the fracture healing	(Dong et al. 2024)

topic search was incorporated into the BIOSIS search to compensate for the absence of sufficiently specific curated terms. Each publication was independently evaluated by three reviewers (HH Y, TL J, and HM D) to extract study characteristics. The results were subsequently compared and discussed, with the consensus findings presented herein. References were exported into the reference management software EndNote X7, where both the duplicate detection function and a manual search were employed to identify and remove duplicates. A relevance assessment was thereafter performed based on predefined inclusion and exclusion criteria. The inclusion criteria were: (1) utilization of gene therapy, (2) focus on bone repair, (3) employment of large animal models, and (4) publication in the English language. The exclusion criteria encompassed: (1) exclusive use of small animal models (rabbits and smaller), (2) studies conducted exclusively in vitro, and (3) review articles, letters to the editor, and other non-research article types.

The advancement of genomics in bone defect

Within the biological sciences, genomics includes several areas of study, such as comparative genomics, functional genomics, and macro-genomics. Next Generation Sequencing (NGS) technology has revolutionized genomics research to detect genomic copy variants under diseases and genetic sequencing. Previous studies have determined the utility of comprehensive genomic analysis in diagnosing bone marrow failure, part of which carry damaging germline mutations in GATA2, RUNX1, DKC1 or LIGIV (Zhang et al. 2015). The advancement of genomics provides new avenues for developing gene-targeting treatment strategy and conducting risk-based screening interventions (Wlodarski 2021). Important information based on post-genomic analysis may help us determine the potential osteoblast differentiation mechanisms and relevant markers for tissue regeneration (Bernardini et al. 2012).

Nowadays, gene delivery in vivo or in vitro regulates specific protein expression to enhance inward growth and potentially biomechanical stability of localized tissues, which has shown a potential for regeneration of musculoskeletal tissues (Collon et al. 2021, Evans 2012). Bone remodeling and regeneration can be alternatively addressed through gene therapy(Ou et al. 2019). Gene therapy offers the advantage of delivering gene sequences locally, which can stimulate bone repair mechanisms (Damiati and El-Messeiry 2021). It employed viral and non-viral vectors accompanied by scaffolds serving as a promising tool for bone repair. Gene delivery methods have considered as promising tactic for producing predominant osteogenic factor BMPs or other factors and delivering target genes using engineered cells. In particular, an ex vivo TGF-β1 gene therapy was applied for treatment of moderate-to-severe osteoarthritis (Grol and Lee 2018). Although viral-based gene delivery vector has gained a huge success in transfection efficiency and stability, the off-target effect, immune related adverse risk and restricted viral tropism are still inevitable events, which limit the further clinical application and development especially for adeno-associated virus vectors (Zhang et al. 2024). There is a growing emphasis on non-viral gene therapy as a safer and more readily translatable alternative for musculoskeletal disorders (Fig. 1). In scenarios where only transient transgene expression is necessary, nucleic acids are delivered either in a "naked" form or incorporated within synthetic carriers such as capsules or nanoparticles (Yin et al. 2014). Ex vivo gene therapy, which integrates cell and gene therapy, offers a potential strategy to address the challenges associated with both approaches. This technique involves extracting cells from the patient or donor, performing transduction or transfection in a laboratory setting, screening for successful genetic modification, and subsequently reintroducing the cells into the patient (Gregory-Evans et al. 2012). Ex vivo regional gene therapy uses genetically altered cells to transport the desired protein to a targeted location of bone repair. Although ex vivo gene therapy is theoretically appealing and has demonstrated success in treating various human conditions, it remains costly, time-consuming, and labor-intensive. Hence, it introduces a range of new safety and regulatory challenges, which significantly impede its widespread clinical application.

In terms of damage repair in bone tissue, it has found that bone morphogenetic proteins (BMPs) family members play vital role in development, homeostasis, and repair of human bone (Wang et al. 2014). Stem cells can be induced to differentiate into osteoblasts and chondrocytes (Damiati and El-Messeiry 2021) by delivering genes of the BMP family, which

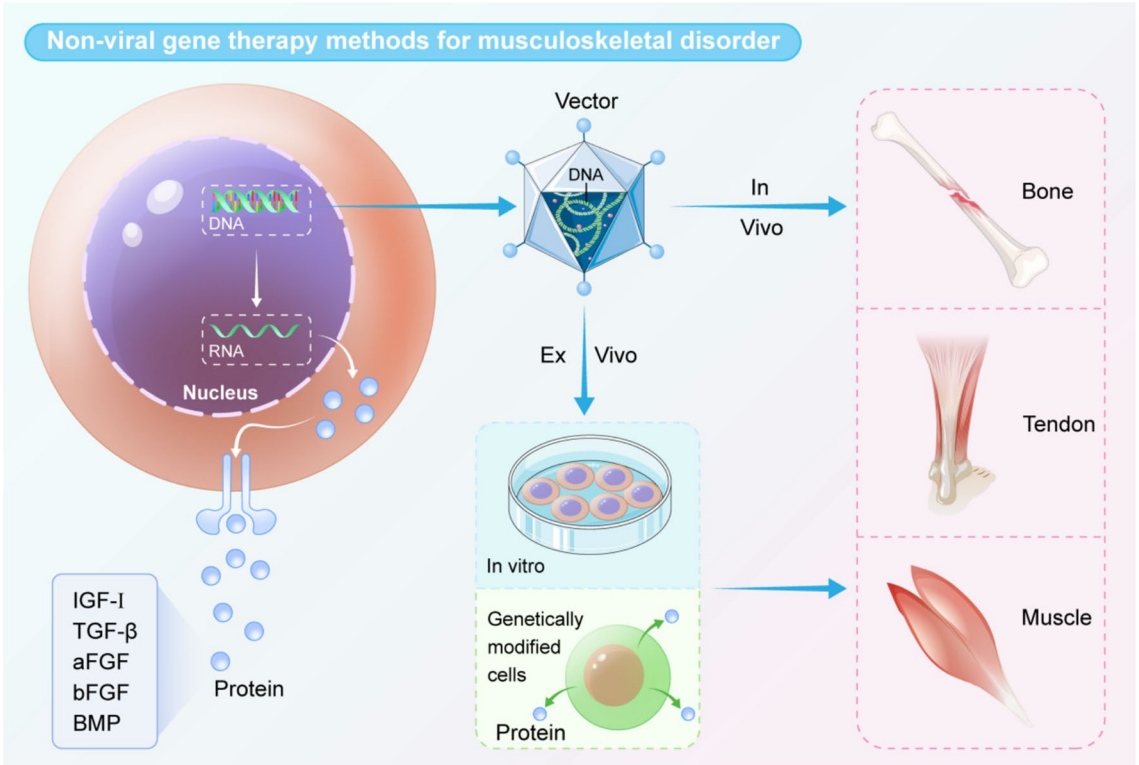

Fig. 1 Non-viral gene therapy methods for musculoskeletal disorder. Nucleic acids are delivered either in a naked form or incorporated within synthetic carriers such as capsules or nanoparticles for treating musculoskeletal injury. Ex vivo gene therapy involves extracting cells from the patient or donor, performing transduction or transfection in a laboratory setting, screening for successful genetic modification, and subsequently reintroducing the cells into the patient with musculoskeletal injury

mediate the expression of BMP-2 (Damiati et al. 2018, Cheng et al. 2019), BM-P3 (Daluiski et al. 2001) and BMP-7 (Al-Jarsha et al. 2018) proteins. Evidence indicated that regional gene therapy using lentiviral vectors containing BMP-2 complementary DNA (cDNA) cures critical-sized bone defects in rodent models and holds promise for future extrapolation for use in humans (Ihn et al. 2021). In addition, injured ligaments and tendons also present a range of regenerative challenges (Zhao et al. 2021). Delivery of cDNA encoding regenerative growth factors to the site of the lesion is important for ligament and tendon repair (Wang et al. 2024). It has been found that after overexpression of TGF-β cDNA in muscle implants, surgically repaired animal tendons showed better mechanical properties and better organized collagen fibers. Surgically repaired animal tendons showed better mechanical properties and better organized collagen fibers (Wu et al. 2017, Wu et al. 2021). Preliminary gene transfer experiments have also been performed in meniscal repair, but as with ligaments and tendons, there appear to be no upcoming human clinical trials (Chen et al. 2021, Atik et al. 2021, Otani et al. 2022). Under severe traumatic conditions, the intrinsic healing capacity of muscle may be compromised, leading to the formation of fibrous scar tissue. It has been found that increased expression of PGC1α by muscle-specific adeno-associated virus (AAV) 8-AUF1 gene therapy improved motor performance and ameliorated skeletal muscle deficits in adult mice (Abbadi et al. 2021).

Epigenomics of bone tissue repair

Epigenomics concerned methylation, acetylation and histone modifications through potentially regulating the osteoblast differentiation pathway to improve

bone injury (Lyu et al. 2019). It suggests that understanding the specific DNA methylation patterns and histone modification mechanisms of bone diseases will further increase our understanding in the pathology and may even lead to the development of new management strategies.

Histone stability was found to be important for maintaining chromatin structure in a lightly stacked state, thereby maintaining active transcription (Bowman and Poirier 2015). Chemical modification of histone proteins results in densely affected chromatin, thereby hindering polymerase transcription (Li et al. 2022). Histone methyltransferases and demethylases regulate histone methylation, thereby inducing repressive transcription (Douillet et al. 2020). As exhibited in Fig. 2A, the ubiquitously transcribed tetrapeptide repeat X chromosome (UTX) was found to erase histone trimethylation (Yang et al. 2015), and Zeste Homolog 2 (EZH2) was demonstrated to catalyze histone trimethylation such as H3K27 (Wang et al. 2021). Experiment results based on EZH1 and EZH2-deficient mice model identified their effect in promoting chondrocyte proliferation (Lui et al. 2016). Histone acetyltransferases (HAT) and histone deacetylases (HDAC) alter the acetylation state of histones (Martins and Histones 2013, Millán-Zambrano et al. 2022). HDAC8 inhibited osteogenesis-related genes expression by removing the acetylation of histone H3K9 (Fig. 2B), inducing transcriptional inhibition during osteogenic differentiation of bone marrow stromal cells (BMSCs) (Fu et al. 2014). In addition, DNA methylation can promote osteogenic differentiation of osteoblasts by increasing the transcription of specific genes, such as Runx2 shown in Fig. 2C (Zhang et al. 2018). Recent epigenetic research has revealed that IL-6 and its soluble receptor (sIL-6R) led to the STAT3-dependent differentiation of human vascular smooth muscle cells (VSMCs) into osteoblast-like cells via JMJD2B/KDM4B-mediated histone demethylation of Runx2 (Kurozumi et al. 2019).

Bone tissue cells rank among the most metabolically active cells in the human body. Osteoblasts and

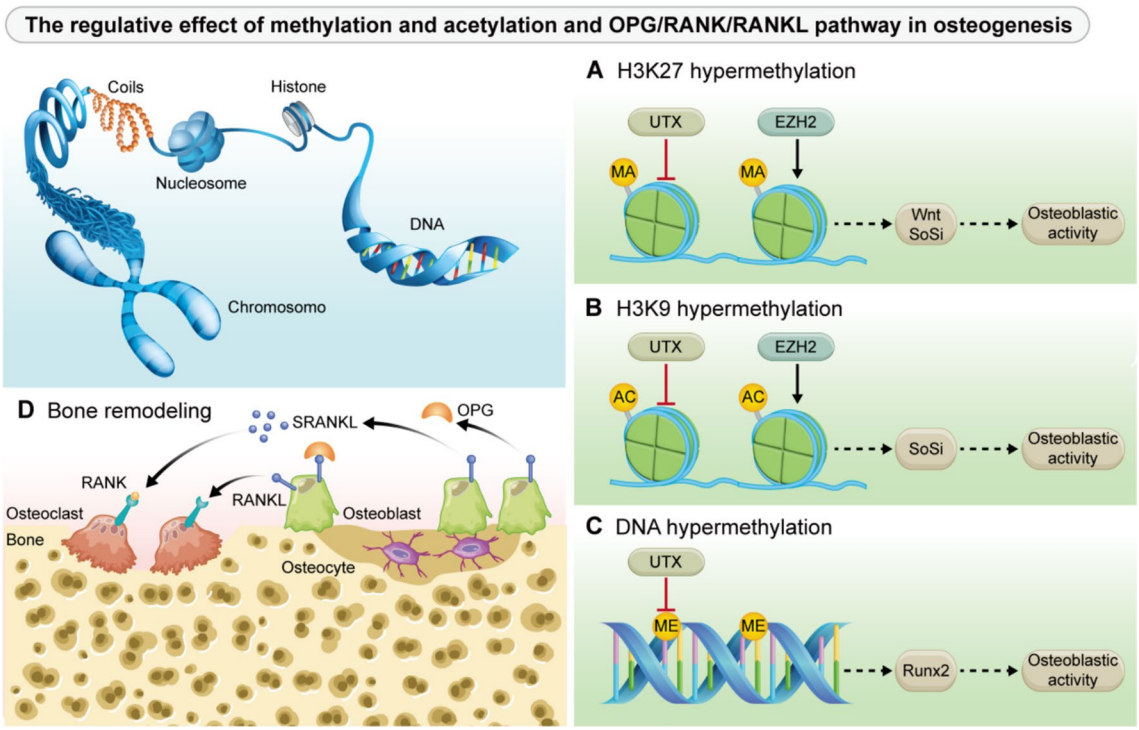

Fig. 2 The regulative effect of methylation and acetylation and OPG/RANK/RANKL pathway in osteogenesis. Methylation, acetylation and histone modifications potentially regulated the osteoblast differentiation to improve bone injury. RANKL is produced by osteoblasts and binds to RANK on the surface of osteoclasts to activate osteoclast gene expression. OPG exerts a negative regulatory effect on the interaction between RANKL and RANK in bone modeling

osteoclasts maintain a dynamic equilibrium essential for bone metabolism. The receptor activator of nuclear factor-kB (RANK) combined with the RANK ligand (RANKL) is crucial for the coupling of osteogenesis and bone resorption (Nakashima et al. 2011). RANKL is produced by osteoblasts and binds to RANK on the surface of osteoclasts to activate osteoclast gene expression (De Leon-Oliva et al. 2023). Numerous studies have demonstrated that osteoprotegerin (OPG), RANK and RANKL regulate osteoclast differentiation and development, thereby influencing their functional activity in Fig. 2D (Boyce and Xing 2008). RANKL binds to RANK on the surface of osteoclasts, promoting their differentiation and activation while inhibiting apoptosis. Conversely, OPG impedes the RANKL-RANK interaction, thereby preventing osteoclast activation, inhibiting their function, reducing bone resorption, and exerting a negative regulatory effect. Following an example of patients with alcohol-induced osteonecrosis of the femoral head (ONFH), it has been found that CpG sites in OPG/RANKL/RANK gene were abnormally methylated based on peripheral blood leukocyte samples (Wang et al. 2021).

Thus, these epigenetic modification mechanisms function in the repair of skeletal tissue and the development of targeted therapies.

Transcriptomics and proteomics of bone tissue healing

To date, about 2,600 mature microRNAs (miRNAs) have been identified in humans, and they have been reported to be involved in the regulation of more than 60% of the encoded genes (Guan et al. 2022). Research has demonstrated that miRNAs are associated with osteoporosis and osteoporotic fractures in both serum and bone samples (Kelch et al. 2017). In the context of physiological fracture healing, miRNAs can influence processes of bone regeneration including angiogenesis and osteogenesis (Fröhlich 2019).

miRNAs are primarily gene silencers, and their expression correlates negatively with the regenerative potential of damaged tissues. miRNAs are not limited to the regulation of musculoskeletal tissue diseases at the level of transcriptomics, but they are also intertwined with proteomics. A series of studies have demonstrated that miRNAs regulate the expression of a range of proteomics (Table 1). In vivo studies have revealed that miR-126 enhances the expression of angiogenesis-related genes during fracture healing, including HIF-1A, Ang1, VEGF-A, and TGF-β1 (Jia et al. 2019). Additionally, miR-29a has been shown to promote matrix mineralization in vitro by targeting DKK1 and SFRP2, thereby upregulating Wnt signaling. This upregulation facilitates matrix mineralization and increases the expression of osteogenic markers such as BMP2, OPN, OCN, and COL1A1 (Roberto et al. 2014). Furthermore, miR-451, a glucose-regulated miRNA, enhances mineralization both in vitro and in vivo by suppressing Odd Skipped Related 1 while promoting the expression of RUNX2 and BMP-4 (Karvande et al. 2018). Lastly, miR-503 facilitates both osteogenic differentiation and mineralization by targeting SMURF1, a known inhibitor of TGF-β/BMP signaling (Sun et al. 2017). In recent years, extensively transcribed lncRNAs have been found to have a variety of biological functions in the mammalian genome in terms of cell differentiation and tissue regeneration (Shan et al. 2021, Loewer et al. 2010). For example, miR-223-3p was controlled by lncRNA MAGI2-AS3, overexpression of which may promote osteogenic marker levels and even the fracture healing by targeting miR-223-3p (Dong et al. 2024).

Transcriptomic approaches, in particular scRNA-seq analysis, examined the fundamental heterogeneity of skeletal lineage cells at the single-cell level and mapped the transcriptomic landscape of vascular, perivascular, and osteoblast populations in mouse bone marrow (Tikhonova et al. 2019). Single-cell, multi-homology analysis of young and old mouse skeletal lineage cells revealed a strong correlation between osteoblast- chondrocyte transmigration (OCT) stem cells and the chondrocytes and osteoblasts with transcriptomic similarities (La Manno et al. 2018, Bergen et al. 2020). Transcriptomic analysis also revealed that tRNA-derived small RNAs (tsRNAs) are significantly enriched after muscle injury and positively correlate with inflammation in vivo, potentially regulating skeletal muscle regeneration (Shen et al. 2023). Subsequently, it was found that 5' tiRNA-Gly induced inflammation as a process involving the TGF-β signaling pathway.

According to Fig. 3, the bone fracture healing process is divided into inflammatory, reparative, and

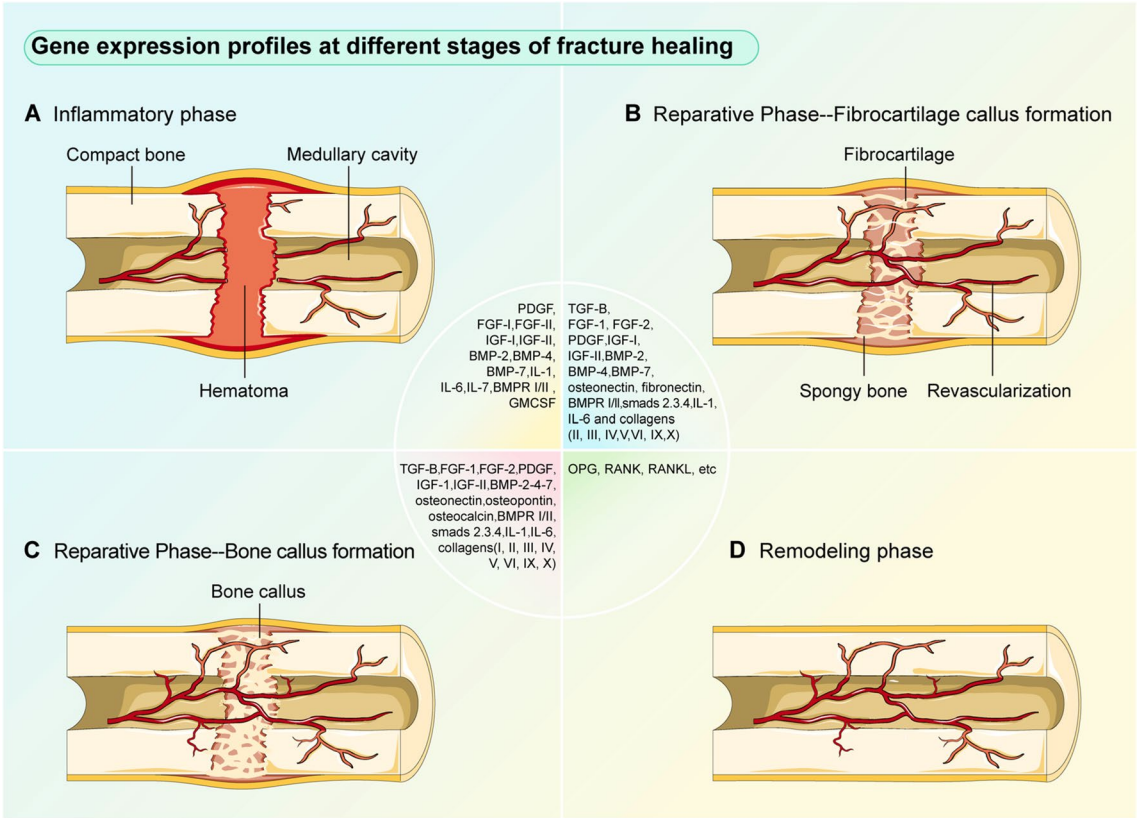

Fig. 3 Gene expression profiles at different stages of fracture healing. The bone fracture healing process included inflammatory, reparative, and remodeling phases. There is variability in gene expression profiles during the different stages of fracture healing mediated by a variety of growth factors, including TGF-β, IGF-I, and BMP, etc

remodeling phases (Mehta et al. 2012). There is variability in gene expression profiles during the different stages of fracture healing mediated by a variety of growth factors, including insulin-like growth factor I (IGF-I) (Kok et al. 2021, Ganguly et al. 2023, Shen et al. 2002), TGF-β (Mukherjee et al. 2012, Yang et al. 2022), acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF) (Chaudhary et al. 2004) and BMP (Zubaidah et al. 2023; Wu et al. 2024). Initially, a coagulation cascade forms the hematoma along with the infiltration of progenitor cells in the trauma (Jiao et al. 2021). These protein molecules act through autocrine and paracrine signaling mechanisms to induce migration, proliferation and differentiation of bone progenitor cells and/or type I collagen synthesis and matrix deposition in mature osteoblasts. These factors are stored in the extracellular matrix during bone formation and are released by the matrix when traumatic damage occurs to initiate bone healing and maintain the cyclic anabolic and catabolic processes that continuously remodel bone (Emecen et al. 2009). At the early reparative phase, a spanning callus takes up most fracture space and serves a primed template for subsequent reparative and remodeling phases. Subsequent to the reparative phase-fibrocartilage callus formation, fibrous tissue and new cartilage begin to form, and blood vessels re-form. Macrophages, chondrocytes, chondroblasts, osteoclasts, fibroblasts, and endothelial cells begin to appear along with TGF-β, FGF-1, FGF-2, PDGF, IGF-I, IGF-II, BMP-2,−4–7, osteonectin, fibronectin, and BMPR I/ll, smads 2,3,4, IL-1, IL-6 and collagens (II, III, IV,V,VI, IX,X) are expressed (Sousa et al. 2022). In the reparative phase-bonycallus formation, intramembranous and endochondral bone is initiated to lay down new woven bone. Macrophages, chondroblasts, chondrocyte-osteoblasts, osteoblasts, and endothelial cells appear successively, accompanied by

the expression of the following genes: TGF-β, FGF-1, FGF-2, PDGF, IGF-1, IGF-II, BMP-2–4, −7, osteonectin, osteopontin, osteocalcin, BMPR I/II, smads 2, 3, 4, IL-1, IL-6, and collagens (I, II, III, IV, V, VI, IX, X).

Glycomics and lipidomics of bone tissue repair

Analysis of the cellular changes that accompany the process of tissue repair with the aim of understanding the energy requirements and lipid signaling of osteoblast during bone repair. In the state of new bone formation and remodeling, the synthetic phase of osteoblast differentiation requires large amounts of energy. The balance of activity between osteoblasts and osteoclasts is responsible for the reparative capacity and the remodeling of the trabecular bone surface (Salhotra et al. 2020).

Intracellular metabolic process of osteoblast

Osteoblasts have metabolic plasticity, suggesting that bone formation is related to the metabolic state (Karsenty and Khosla 2022). The main source of energy substrate for osteoblasts is glucose. Glucose transporter proteins are the major glucose transporter protein in osteoblasts and involves two mechanisms to stimulate osteoblast differentiation and bone formation (Arponen et al. 2022). On the one hand, inhibition of AMPK-dependent proteasomal degradation of RUNX2 (Jang et al. 2011). On the other hand, promotes collagen matrix production by inducing mTORC1-mediated protein synthesis. Pyruvate is metabolized to lactate during glycolysis, while it is metabolized to acetyl-coA into the TCA cycle under aerobic conditions. Glycolysis levels in osteoblasts are regulated by a variety of factors, including inducible factors, hormones, and signaling pathways. For example, HIF1α was found to induce glycolysis in mouse osteoblasts to increase bone mass (Regan et al. 2014). Parathyroid hormone PTH increases glycolysis and thus promotes the release of osteogenic factors from osteoblasts (Alekos et al. 2023, Maridas et al. 2019). Sustained activation of Notch2 signaling in osteoblasts induces bone loss in mice (Zanotti et al. 2017). WNT3A/LRP5 signaling regulates osteoblast metabolism by stimulating aerobic glycolysis, a mechanism mediated by $mTORC_2$-AKT signaling (Frey et al. 2018). Except for glucose, which serves as the primary nutrient for osteoblast lineages, previous evidence underscores the significance of amino acid metabolism in supplying the energy essential for the optimal functioning of osteoblasts. Notably, glutamine (Gln) has been identified as a critical substrate for differentiation and activation of osteoblasts. Emerging research has demonstrated that WNT-mTORC1 signaling enhances the protein expression of enzymes involved in glucose and Gln metabolism (Dirckx et al. 2019). Gln also plays diverse roles in the biosynthesis of glutathione (GSH), an antioxidant that safeguards cells against oxidative stress (Yoo et al. 2020).

Inflammatory phases of bone tissue repair under metabolomics

Following bone injury, inflammatory processes are essential for tissue repair, and changes in the levels of their metabolites are involved in the healing and regeneration of bone tissue. With recent advances in mass spectrometry, it is possible to characterize the metabolism of bone regeneration in detail. For example, differentiated osteoblasts are also largely dependent on glycolysis and oxidative phosphorylation (Ejtehadifar et al. 2015). Lactate promotes extracellular matrix synthesis and healing tissue progression in an autocrine/paracrine manner during fracture healing (Fan et al. 2021, Oryan et al. 2023).

The process of bone repair requires the involvement of osteoblasts, whose differentiation is dependent on the microenvironment provided by surrounding ecological niche cells, such as inflammatory cells and endothelial cells (Cole et al. 2023). Acute bone injury leads to rupture of blood vessels within the bone and in the surrounding soft tissues, resulting in the formation of hematomas (Alinejad et al. 2020). Hematomas are characterized by local tissue hypoxia and low pH (Duan et al. 2022). Hypoxia affects metabolic redistribution of cells and activates inflammatory cells, including recruitment of macrophages and influx of neutrophils. Typically to ameliorate tissue hypoxia, VEGF expression rises in response to hypoxia inducible factors (HIFs) to increase erythropoiesis and angiogenesis (Liu et al. 2022) (Fig. 4A). Concomitantly, up-regulation of bone morphogenetic protein 4 (BMP4) transcripts is affected

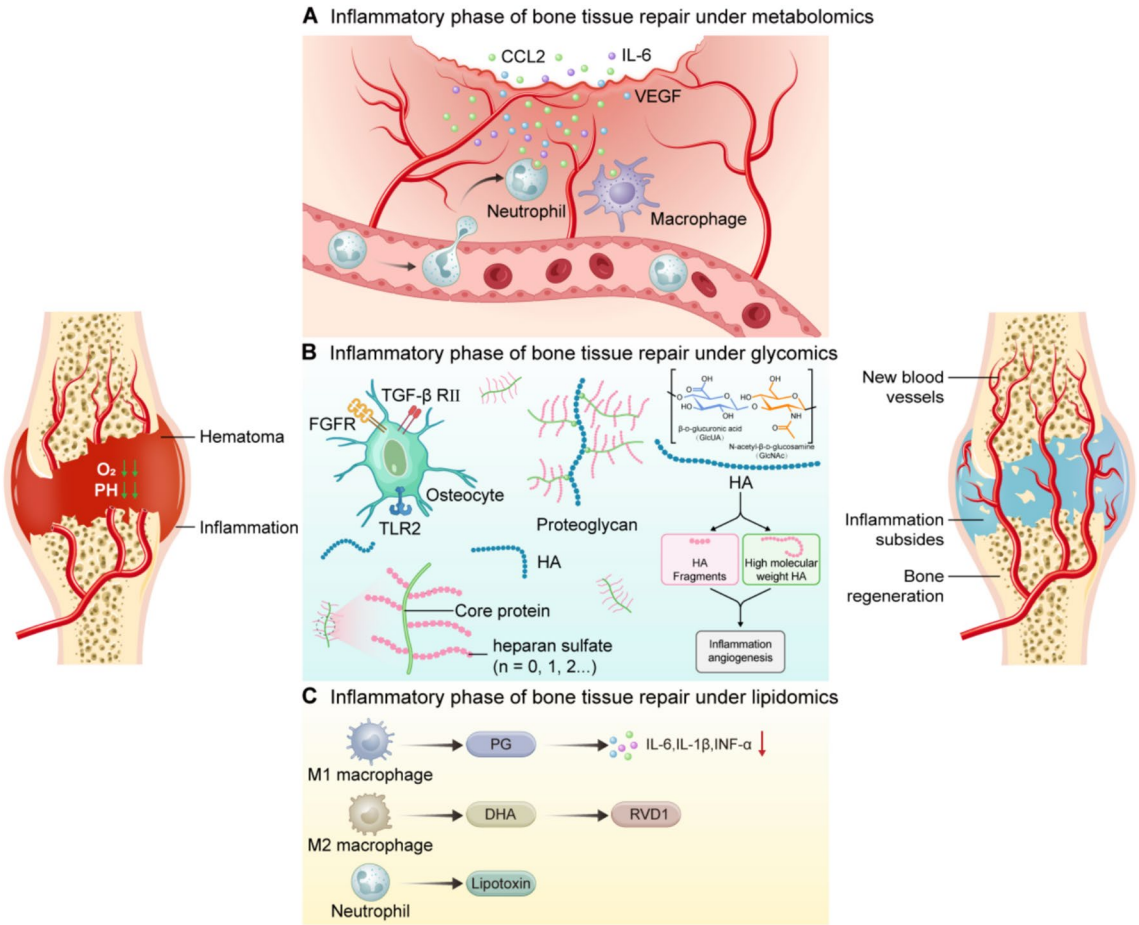

Fig. 4 Inflammation phases of bone tissue repair estimated by multi-omics. As the formation of hematoma due to fracture, it followed by local tissue hypoxia and low pH. At this inflammatory stage, many immune cells remove injured tissue and secrete stimulatory factors to recruit cells from the periosteum environment. (**A**) Based on metabolomics, hypoxia affects metabolic redistribution of cells and activates inflammatory cells, including recruitment of macrophages and influx of neutrophils. (**B**) Based on glycomics, proteoglycans, glycolipids and HA constitute the glycocalyx on the cell surface, where their shedding and interaction with chemokines, receptors and other molecules in the endosteal and mineralized areas of the bone mediate the inflammatory response. (**C**) Based on lipidomics, immune cells release a variety of fatty acids to modulate the inflammatory response after bone injury

by hypoxia (Pulkkinen et al. 2021). For example, large accumulations of inflammatory cells promote chemokines such as macrophages and neutrophils. Massive aggregation promotes the secretion of chemokines such as IL-6 and CCL2 (Robert et al. 2022). Together, the secretion of these bone-enabling and pro-angiogenic factors constitutes a pro-regenerative milieu microenvironment that promotes osteoblast differentiation and ultimately bone repair.

Inflammatory phases of bone tissue repair under glycomics

The inflammatory phase of bone tissue regeneration involves inflammatory response and abatement, and glycans play an important role in this process (Fig. 4B). The repair phase is characterized by neoangiogenesis and extracellular matrix (ECM) secretion (Goonoo and Bhaw-Luximon 2019). As the main component of the ECM, proteoglycan is covalently

linked to a core protein by one or more glycosaminoglycans. Proteoglycans, glycolipids and hyaluronic acid (HA) constitute the glycocalyx and are present on the cell surface, where their shedding and interaction with chemokines, receptors and other molecules in the endosteal and mineralized areas of the bone mediate the inflammatory response (Mende et al. 2016, Jackson et al. 1991). Of these, hyaluronic acid and heparan sulphate have been most studied in the context of inflammation. HA is the simplest glycosaminoglycan (GAG) in nature, consisting of repeating dimers of GIcUA and GIcNAC and is an important molecule for the ECM (Dicker et al. 2014). The biological function of HA in tissues is based on interactions among HA, HA-binding proteins and proteoglycans together to form a scaffolding network (Stecco et al. 2022). Hyaluronic acid biosynthesis is increased during inflammation and cancer and is regulated by cytokines and growth factors. Upon breakdown by hyaluronidase, HA fragments smaller than 200 kDa trigger inflammation and promote angiogenesis. However, high molecular weight HA exhibits anti-inflammatory activity, anti-angiogenesis, and induces tissue repair processes such as wound healing (Hintze et al. 2014; Nakato and Li 2016). CD44, the main receptor for HA associated with musculoskeletal tissues, is present on the cell membrane of inflammatory cells. Cells are anchored to the matrix by HA interaction with CD44.

The major proteoglycan in bone is heparan sulfate, a highly sulfated glycosaminoglycan that plays a role in a variety of bone physiological functions (Rodgers et al. 2008), osteogenesis regulation (Jackson et al. 2006), skeletal development and growth (Huegel et al. 2013). Heparan sulfate has been shown to interact with with growth factors and growth factor receptors (Gómez Toledo et al. 2021). Lack of heparan sulfate production leads to excessive bone morphogenetic protein signaling and can cause ectopic cartilage formation (Huegel et al. 2013). In addition, acetylheparan sulfate may be used as a potentially novel therapeutic agent to support alveolar bone maintenance and promote bone formation (Miguez et al. 2023).

Inflammatory phases of bone tissue repair under lipidomics

Decreased inflammation following a pro-inflammatory phase may improve bone tissue regeneration. As part of the metabolites, lipids may characterize the inflammatory regression, especially unsaturated fatty acids (Fig. 4C). Prostaglandins (PG) can be used to modulate the inflammatory response during bone repair. The 15d-PGJ2 promotes the catabolism of inflammatory factors and exhibits anti-inflammatory properties (Buckner et al. 2013, Shibata et al. 2002). For example, rats with femoral defects were treated with collagen sponges containing free 15d-PGJ2, and inflammatory factors were found to be IL-6, IL-1β, and TNF-α expression was reduced, and the level of the bone regeneration molecule BMP-6 was upregulated, promoting bone formation (Tang et al. 2017). Resolvin D1 (RvD1), a docosahexaenoic acid (DHA) metabolite, improves bone formation in femoral defects in rats when delivered using chitosan scaffolds (Werz et al. 2018, Vasconcelos et al. 2018). In addition, direct delivery of oleic acid also promotes bone repair for use (Cardoso et al. 2017).

In addition, immune cells release a variety of fatty acids to modulate the inflammatory response after bone injury. For example, 15d-PGJ2 and RvD1, described previously, are secreted by M1 macrophages and released by M2 macrophages, respectively, to promote bone healing. In addition, lipoxins can be released by neutrophils. For example, with the help of neutrophil carriers, the lipoxin A4 analog, benzo-lipoxin A4, improves the regeneration of hard and soft tissues lost due to periodontitis in pigs (Van Dyke et al. 2015).

Lipids also modulate the expression of immune cell populations. The PGI2 receptor (IP) has anti-inflammatory effects and immunosuppressive functions, and Iloprost is a synthetic analog of PGI2. Treatment with Iloprost resulted in a decrease in CD8 + IFNγ + T cells and M1 macrophages and an increase in M2 macrophages (Wendler et al. 2019). It is well known that M1 macrophages are pro-inflammatory and M2 macrophages are anti-inflammatory, while CD8 + T cells exert a cytotoxic effect by producing interferon (IFN-γ). This enhanced switch of pro-inflammatory to anti-inflammatory macrophage phenotype and immunosuppression improved femur fracture repair.

Computational modeling and bioinformatics in bone tissue repair

Bioinformatics tools and machine learning-based algorithms were employed to reveal the pathological

and molecular mechanisms involved in the process of tissue injury and repair, which can help develop therapeutic agents to promote bone tissue healing and regeneration.

A study explored the effect of age on serotonergic axonal regeneration and wound healing by combining the regeneration and healing process after spinal cord injury and the BioSignal database, which was analyzed by RNA sequencing, mapped to the Mouse GrCm38 genome, and processed using the Seurat software package to screen genes and cells for in-depth analysis. This revealed the trends of gene expression and related biological processes in cell populations under conditions at different time points, providing new targets and strategies for therapeutic neural tissue repair.

Using machine learning algorithms to integrate disparate histological datasets and identify robust biomarkers associated with the tissue repair process, facilitating the development of personalized therapeutic strategies. Machine Learning (ML) algorithms include supervised and unsupervised learning techniques for processing and analyzing large-scale multi-omics datasets. In the context of histology integration, crosstalk-based integration approaches combine data matrices to develop models, while model-based integration approaches build final models based on the creation of multiple intermediate models. These algorithms can be used for phenotype prediction, pattern and association analysis in the data, and the development of a variety of modeling frameworks that contribute to the discovery of new or known biomarkers associated with bone tissue regeneration and repair (Reel et al. 2021). For example, Burroughs et al. used a novel combinatorial chemical-conformal screening platform, ChemoTopoChip, to identify suitable bone regeneration materials for human immortalized mesenchymal stem cells (hiMSC) and human macrophage responses. This machine learning allows us to explore the relative cellular guidance of morphology-material combinations. Development of optimal ML algorithms to be applied to treatment regimens at different stages of distal radius fracture healing (Burroughs et al. 2021). In addition to this, machine learning identification of four-pseudogene classifiers can be used as novel prognostic markers

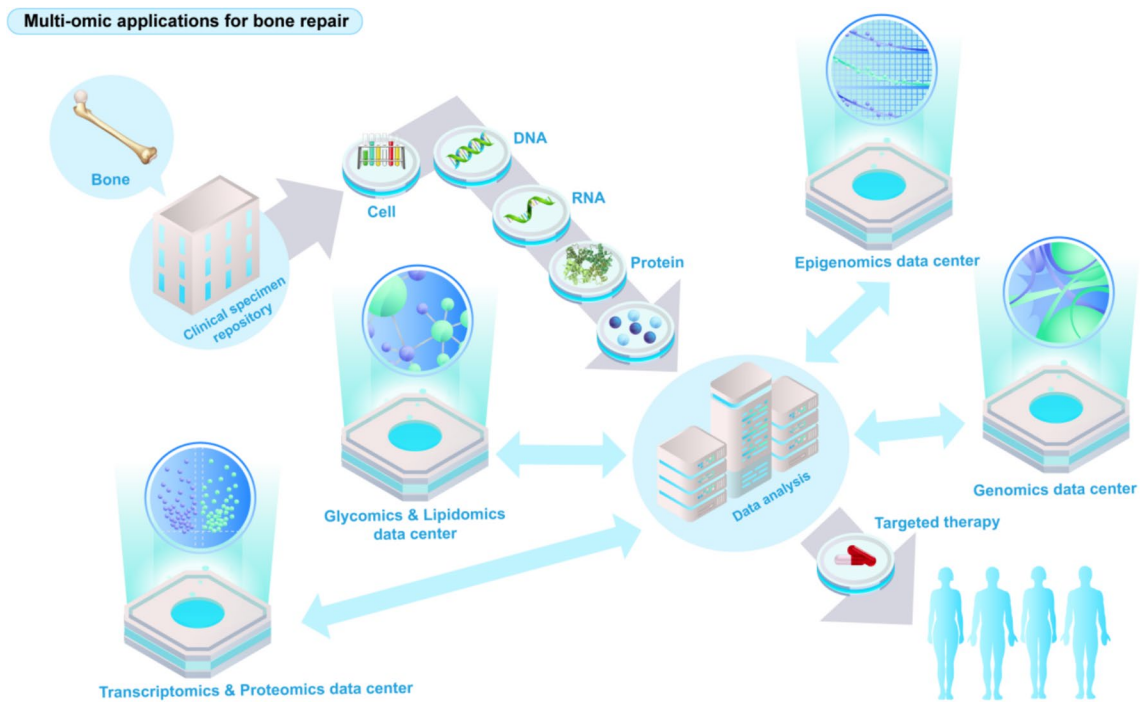

Fig. 5 Graphic abstract

for osteosarcoma survival, potentially providing new ideas for the tissue engineering of tumor-associated bone defects (Liu et al. 2019).

Conclusion and future direction

In recent decades, the omics-based study has been treated to find promising therapeutic molecules during bone osteogenesis. In this review, we are the first to summarize the effects of multiomics from different perspectives concerning genomics, epigenomics, transcriptomics, proteomics, glycomics, lipidomics on the bone tissue repair. Diverse RNAs, proteins and epigenomic modification serve as biomarkers in the process of bone osteogenesis. Despite significant advancements in bone tissue engineering, numerous challenges persist in identifying optimal bone implants for clinical applications. A variety of materials, including polymers and metals, have been employed in bone tissue engineering, each presenting distinct advantages and limitations. At the genomic level, gene therapy has attracted widespread interest in regenerative orthopedics. It has proven to be an effective tool for elucidating the processes of osteogenesis and bone healing, as well as offering innovative strategies for controlling bone infections. Nonetheless, the use of gene therapy in the clinic has not yet become mainstream, in part because the gene therapies approved to date are expensive and require large numbers of systemic deliveries or ex vivo expansions of autologous cells. In contrast, most clinical applications in orthopedics rely more on the local application of relatively inexpensive tissue materials. In a word, considerable progress has been made in the areas of bone healing and cartilage repair, giving optimism for future clinical developments. In the future, the application of advanced technology is anticipated to extend beyond understanding osteogenesis through the generation of genetically modified cells, such as mesenchymal stem cells (MSCs), to include in vivo therapeutic gene editing in defective bone cells to regulate its intracellular metabolic, inflammatory, and gene expression processes (Fig. 5).

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval N/A.

Conflicts of interest The authors declare no competing interests.

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