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Review

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Influence of pathological microenvironments on mesenchymal stem/stromal cell fate: role of long non-coding RNAs in bone-related diseases

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Abstract: The bidirectional relationship between pathological microenvironments and mesenchymal stem/stromal cells (MSCs) is known as a pivotal factor influencing the progression of bone-related disease and therapeutic outcomes. MSCs, characterized by their remarkable plasticity and excellent immunomodulatory abilities, play central roles in various physiological and pathological processes, especially in bone regeneration and repair. Under pathological conditions, such as osteoarthritis, osteoporosis, or bone tumors, the tissue microenvironment can significantly alter MSC behavior, leading to impaired differentiation, dysregulated immune responses, or abnormal tissue remodeling. This dynamic relationship is regulated by diverse molecular signals, where long non-coding RNAs (lncRNAs) emerge as critical regulators of MSC biology. LncRNAs influence MSC differentiation, immunomodulatory functions, and responses to microenvironmental cues through diverse molecular mechanisms. The systematic review elucidates the roles of various lncRNAs involved in different aspects of MSC biology under pathological conditions and their potential as therapeutic targets or biomarkers for bone-related disorders.

Key words: Mesenchymal stem/stromal cells; Long non-coding RNA; Microenvironment; Cell Differentiation; Bone disease

1 Introduction

Mesenchymal stem/stromal cells (MSCs) possess remarkable capability for self-renewal and multilineage differentiation, serving as key players in tissue repair and regeneration processes. Their fate determination and functional properties are intricately linked to the surrounding microenvironment, particularly under pathological conditions (Uccelli et al., 2008). In bone-related diseases, the dynamic interplay between MSCs and the local pathological microenvironment is critical in disease progression and potential therapeutic interventions. This report systematically examines the complex interplay between disease-specific microenvironmental alterations and MSC fate in various bone pathologies, with an emphasis on the regulatory roles of long non-coding RNAs (lncRNAs). LncRNAs function as essential integrators linking the pathological environment to MSC behavior (Ferrer and Dimitrova, 2024). Their responsiveness to microenvironmental stress and ability to modulate gene expression through various downstream pathways allow them to reprogram MSC proliferation, differentiation and secretome profiles in response to disease-associated signals. Recent

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advances have revealed that lncRNAs function as critical mediators in this relationship, responding to microenvironmental cues and subsequently orchestrating MSC responses through various molecular mechanisms including competitive endogenous RNA interactions, epigenetic regulation, and the modulation of key signaling pathways (Table 1).

2 Mesenchymal stem cell biology and function in bone homeostasis

Mesenchymal stem/stromal cells are multipotent progenitor cells characterized by self-renewal capacity and the ability to differentiate into various cell types, including osteoblasts, chondrocytes, adipocytes, and myocytes (Kfoury and Scadden, 2015). They play fundamental roles in maintaining tissue homeostasis, particularly in the skeletal system where they serve as the primary source of bone-forming cells (Sui et al., 2020). Bone marrow-derived MSCs (BM-MSCs) are widely recognized as main contributors to osteoblast populations in vivo and have become increasingly important in cell-based therapies due to their relative accessibility and fewer side-effects following transplantation (Lin et al., 2019). The differentiation potential of MSCs is tightly regulated by complex signaling networks that respond to microenvironmental cues. Under physiological conditions, MSCs maintain a balance between different lineage commitments, particularly between osteogenic and adipogenic differentiation. This equilibrium is critical for proper bone homeostasis and remodeling (Hoshiba et al., 2012). Beyond their direct contribution to bone formation through differentiation, MSCs also exert significant paracrine effects that in11fluence the surrounding microenvironment. They do so by secreting various bioactive factors including cytokines, chemokines, growth factors, and extracellular vesicles that regulate immune responses, angiogenesis, and the activity of resident cells (Cheng et al., 2020). This secretory function enables MSCs to coordinate tissue responses to injury or disease, making them critical players in both bone homeostasis and pathological processes.

The function of MSCs is not intrinsically fixed but rather dynamically responsive to surrounding environmental factors. This plasticity allows them to adapt their behavior according to local tissue needs, which is particularly relevant in pathological contexts (Rolandsson et al., 2021). For instance, in the early inflammatory phase, MSCs can promote appropriate immune responses by enhancing local inflammation when inflammatory cytokines like γ-interferon and tumor necrosis factor-α (TNF-α) are present at lower concentrations (Bernardo and Fibbe, 2013). As inflammation progresses and these cytokine levels increase, MSCs transition to an immunosuppressive phenotype, releasing factors such as transforming growth factor-β (TGF-β), indoleamine 2,3-dioxygenase, inducible nitric oxide synthase, and prostaglandin E2, that suppress T cell activation and proliferation while promoting regulatory T cell expansion. The remarkable adaptability of MSCs to changing microenvironments makes them particularly valuable for therapeutic applications but also subjects them to dysregulation under pathological conditions. Thus, understanding the bidirectional relationship between MSCs and their microenvironment is essential for developing effective treatments for bone-related diseases.

3 Pathological microenvironments in bone-related diseases

Bone-related pathologies create distinctive microenvironmental alterations that profoundly affect MSC behavior and fate determination. These include complex changes in cellular composition, soluble factors, extracellular matrix properties, and mechanical forces, collectively creating disease-specific signatures that drive abnormal MSC responses and contribute to disease progression.

3.1 Inflammatory microenvironments

Table 1 LncRNA regulated in pathological conditions and functions in MSCs

LncRNA	Regulation	Function	Molecular mechanism	Type of MSCs	Related disease	PMID
H19	Down	Promote osteogenesis, inhibit adipogenesis	*miR-541-3p*/ Wnt/β-catenin axis	Rat BMSCs	Osteoporosis	34311444
	Up	Inhibit osteogenesis	*miR-29b-3p*/Dkk1/β-catenin axis	Rat BMSCs	Osteoporosis	38685675
	Down	Promote osteogenesis	*miR-532-3p*/SIRT1 axis	hBMSCs	Osteoporosis	33577975
		Engineer ECM	*miR-29c*	hBMSCs	Osteoporosis	36882843
	Down	Inhibit proliferation, inhibit differentiation	*miR-19b-3p*	hBMSCs	Osteoporosis	31918667
MALAT1	Down	Promote osteogenesis	GATA4/KHSRP/NEDD4 axis	hBMSCs	Osteoporosis	37156809
	Down	Promote osteogenesis	*miR-217*/Akt3 axis	MC3T3-E1	Osteoporosis	35030644
	Down	Promote osteogenesis	*miR-124-3p*/IGF2BP1/Wnt/β-catenin axis	hBMSCs	Osteoporosis	34962086
	Down	Promote osteogenesis	*miR-96*/OSX axis	hBMSCs	Osteoporosis	34456284
	Down	Promote osteogenesis	*miR-143*/OSX axis	hBMSCs	Osteoporosis	29741283
	Down	Promote osteogenesis, inhibit apoptosis	*miR-485-5p*/ Wnt7b	MC3T3-E1	Osteoporosis	36760811
	Down	Inhibit osteogenesis	Mapk signaling pathway	Rat BMSCs	Osteoporosis	31210287
	Down	Promote osteogenesis	*miR-214*/ATF4 axis	hBMSCs	SANFH	31678133
	Up	Promote transformaton	Activate LTBP3	hBMSCs	Multiple myeloma	25187517
Xist	Up	Inhibit osteogenesis		Rat BMSCs	Osteoporosis	30651866
	Up	Inhibit osteogenesis	*miR-29b-3p*/Nnmt axis	hBMSCs, Rat BMSCs	Osteoporosis	34486487
		Inhibit osteogenesis	*miR-19a-3p*/Hoxa5 axis	hBMSCs, mBMSCs	Osteoporosis	33014522
	Up	Inhibit osteogenesis	IRF-1/*miR-450b*/FBXW7 axis	hBMSCs	Osteoporosis	36800052
	Down	Promote osteogenesis	*miR-9-5p*	hBMSCs	Osteoporosis	32389806
	Up	Inhibit chondrogenesis	TAF15/FUT1 axis	hBMSCs	Osteoarthritis	35402663
MEG3		Promote osteogenesis	DEPTOR/BMP4	hBMSCs	Osteoporosis	29973283
	Up	Inhibit osteogenesis	*miR-133a-3p*	hBMSCs, mBMSCs	Osteoporosis	28320084
	Down	Promote osteogenesis	SOX2/BMP4 axis	hBMSCs	Multiple myeloma	25753650

To be continued

Table 1 (continued)

LncRNA	Regulation	Function	Molecular mechanism	Type of MSCs	Related disease	PMID
SNHG1	Up	Inhibit osteogenesis, promote adipogenesis	Ptbp1/Dnmt1/ Opg axis	mBMSCs	Osteoporosis	34854215
	Up	Inhibit osteogenesis	Histone modification	hBMSCs	Osteonecrosis	34455928
	Up	Inhibit osteogenesis	p38/Mapk/Nedd4	BMSCs	Osteoporosis	31055087
SNHG14	Down	Promote osteogenesis	*miR-185-5p*/ WISP2 axis	hBMSCs	Osteoporosis	33928771
	Up	Promote osteogenesis	miR-2861	hBMSCs	Osteoporosis	32770994
DANCR	Up	Inhibit osteogenesis	*miR-320a*/Wnt/β-catenin axis	hBMSCs	Osteoporosis	32778797
	Up	Inhibit osteogenesis	FOXO1	MSCs	Prostheses	29338713
HCG18	Up	Inhibit osteogenesis	*miR-30a-5p*/NOTCH1 axis	hBMSCs	Osteoporosis	33176682
LINC00205	Up	Inhibit osteogenesis	*miR-26b-5p*/KMT2C axis	hBMSCs	Osteoporosis	37016415
PCBP1-AS1	Up	Inhibit osteogenesis	*miR-126-5p*/PAK2 axis	hBMSCs	Osteoporosis	37306572
KCNQ1OT1	Down	Promote osteogenesis	*miR-205-5p*/ RICTOR	hBMSCs	Osteoporosis	35341776
	Down	Promote osteogenesis	*miR-421-3p*/mTOR axis	MC3T3-E1	Osteoporosis	36759677
TIMP3	Down	Promote osteogenesis	*miR-214*/Smad4 axis	Rat BMSCs	Osteoporosis	38824271
ROR	Down	Promote proliferation, inhibit apoptosis	*miR-145-5p*	MC3T3-E1	Osteoporosis	34617877
LINC00963	Down	Promote osteogenesis	*miR-760*/ETS1	hBMSCs	Osteoporosis	34184952
LOXL1-AS1	Up	Inhibit osteogenesis, promote adipogenesis	*miR-196a-5p*/ HMGA2 axis	hBMSCs	Osteoporosis	32651705
GAS5	Down	Promote osteogenesis	*miR-498*/RUNX2	hBMSCs	Osteoporosis	31599401
XIXT	Down	Promote osteogenesis	*miR-30a-5p*	hBMSCs	Osteoporosis	31696458
MIAT	Up	Inhibit osteogenesis, inhibit proliferation, promote apoptosis	*miR-150-5p*	Rat BMSCs	Osteoporosis	35282774
LINC02381	Up	Inhibit osteogenesis	*miR-21*	hUC-MSCs	Osteoporosis	34778905
SNHG16	Down	Promote osteogenesis	*miR-485-5p*/BMP7 axis	hBMSCs	Osteoporosis	33179372
LNC_000052	Up	Inhibit osteogenesis	*miR-96-5p*/Pik3r1 axis	Rat BMSCs	Osteoporosis	32968049
MIR22HG	Down	Promote	PTEN/AKT	hBMSCs	Osteoporosis	32732881

		osteogenesis	pathway			

To be continued

Table 1 (continued)

LncRNA	Regulation	Function	Molecular mechanism	Type of MSCs	Related disease	PMID
ORLNC1	Up	Inhibit osteogenesis, promote adipogenesis	*miR-296*/Pten axis	mBMSCs	Osteoporosis	30638773
HOTAIR	Up	Inhibit osteogenesis	Wnt/β-catenin pathway	Rat BMSCs	Osteoporosis	31539110
	Up			mBMSCs	SONFH	33324039
LINC00665	Up	Inhibit chondrogenesis, inhibit proliferation	*miR-214-3p*	BMSCs	Osteoarthritis	38167456
HOTTIP	Up	Reduce cartilage-specific genes	*miR-455-3p*/CCL3 axis	hBMSCs	Osteoarthritis	31508417
GAS5	Down			hBMSCs	ONFH	35392165
NORAD	Down	Improve DEX-induced inhibition of proliferation and differentiation, promote apoptosis	*miR-26a-5p*	hBMSCs	SONFH	33413642
DGCR5	Up	Encode polypeptide	Encode RIP	hBMSCs	SONFH	37573506
AWPPH	Down		RUNX2	hBMSCs	ONFH	31853285
RP11-154D6	Down	Promote osteogenesis, inhibit adipogenesis		hBMSCs	SONFH	31190361
Miat	Up	Inhibit osteogenesis		Rat BMSCs	ONFH	30970282
LINC00473	Down	Promote migration, proliferation, inhibit apoptosis	PEBP1/AKT axis	hBMSCs	SONFH	33236136,32829248
LOC103691165	Up	Promote osteogenesis		Rat BMSCs	Bone fracture	36879890
LOC103691336	Up (in implants)	Promote osteogenesis	*miR-138-5p*/Bmpr2 axis	Rat BMSCs	Bone fracture	31081160
PRNCR1	Up	Inhibit osteogenesis	*miR-211-5p*/CXCR4 axis	MSCs	Prostheses, osteolysis	29775758,29752342
POIR	Down	Promote osteogenesis	*miR-182*/FOXO1	hPDLSCs	periodontitis	27512949
ANRIL	Down	Promote osteogenesis	*miR-7*/NF-κB pathway	hPDLSCs	Periodontitis	34868829
ENST00000563492	Down	Promote osteogenesis-angiogenesis coupling process	*miR-205-5p*	hBMSCs	Bone nonunion	32587236
FAM83H-AS1	Down	Promote osteogenesis	*miR-541-3p*/WNT3A axis	hBMSCs	Osteomyelitis	31871129
HOXC-AS3		Promote osteogenesis	HOXC10	hBMSCs	Multiple myeloma	30353595

To be continued

Table 1 (continued)

LncRNA	Regulation	Function	Molecular mechanism	Type of MSCs	Related disease	PMID
RUNX2-AS1	Up	Inhibit osteogenesis	RUNX2	hBMSCs	Multiple myeloma	29895968
ZEB1-AS1	Up	Promote proliferation	IL-11	hBMSCs	B-ALL	28861713

Shown are the long non-coding RNAs, their regulatory changes, associated functions in mesenchymal stem cell lineage commitment, underlying molecular mechanisms, MSC sources, related diseases, and the corresponding PubMed identifiers (PMIDs). Abbreviations: ECM: extracellular matrix, DEX: dexamethasone, hUC-MSCs: human umbilical cord mesenchymal stem cells, hPDLSCs: human periodontal ligament stem cells, SANFH: steroid-induced avascular necrosis of femoral head, SONFH: steroid-induced osteonecrosis of the femoral head, B-ALL: B-cell acute lymphoblastic leukemia.

Inflammation, a common feature across numerous bone-related disorders, creates a microenvironment characterized by elevated levels of pro-inflammatory cytokines and immune cell infiltration (Zhou et al., 2019). The inflammatory milieu significantly impacts the behavior of MSCs, altering their differentiation capacity, secretory profile, and immunomodulatory functions (Sun et al., 2014). MSCs demonstrate remarkable sensitivity to inflammatory signals, adapting their responses based on the specific inflammatory context. For instance, the nuclear factor kappa-B (NF-κB) pathway serves as a crucial inflammatory mediator that influences MSC differentiation by modulating transcription factor accessibility at osteogenic gene promoters (Zhu et al., 2019). Chronic inflammation, characteristic of many bone diseases, creates a particularly challenging microenvironment for MSCs (Lee et al., 2021). Persistent exposure to pro-inflammatory signals can impair the regenerative capacity of MSCs, promoting senescence, reducing differentiation potential, and altering secretory profiles (Kushioka et al., 2023). These changes contribute to a cycle of ongoing tissue damage and impaired repair function that perpetuates disease progression. It is worth noting that the impact of the inflammatory microenvironment on MSCs is highly context-dependent and often biphasic. During early inflammation characterized by low levels of pro-inflammatory cytokines, MSCs may adopt a pro-inflammatory phenotype that supports appropriate immune responses. As inflammation persists and cytokine concentrations increase, MSCs typically transition toward an immunosuppressive state, secreting anti-inflammatory factors that promote resolution and tissue repair (Wang et al., 2022). This dynamic response highlights the remarkable plasticity of MSCs and their ability to adapt to changing microenvironmental conditions. Understanding the specific effects of inflammatory microenvironments on MSC function is therefore essential for developing effective therapeutic strategies for bone-related disorders.

3.2 Hypoxic microenvironments

Hypoxia constitutes another significant feature of many pathological bone microenvironments, particularly in conditions like fractures, tumors and inflammatory disorders where vascular supply is compromised (Narasimhan et al., 2024). The complex relationship between oxygen tension and MSCs influences their survival, proliferation, differentiation, and secretory capabilities. In various types of malignant hematologic tumors, hypoxia emerges as a defining characteristic that affects both malignant cells and the surrounding stromal components, including MSCs (Tian et al., 2022). Hypoxia-inducible factors (HIFs) function as master regulators of cellular adaptation to low-oxygen conditions and can induce the expression of specific lncRNAs in MSCs (Ye et al., 2021). Interestingly though, moderate hypoxia may benefit certain aspects of MSC function. Several studies have demonstrated that controlled hypoxic preconditioning can enhance the survival, proliferation and paracrine effects of MSCs, potentially improving their therapeutic efficacy (Xue et al., 2024). This observation has led to the development of hypoxic preconditioning protocols for MSC-based therapies, particularly for applications in ischemic or poorly vascularized tissues (Ishiuchi et al., 2020).

Nonetheless, more studies are necessary to evaluate the fate of MSCs under severe or prolonged hypoxia.

3.3 Altered extracellular matrix

The extracellular matrix (ECM) represents a critical component of the bone microenvironment, providing not only structural support but also biochemical and biomechanical cues that profoundly influence MSC behavior (Dong et al., 2020). Pathological conditions frequently alter the composition, organization and mechanical properties of the ECM, creating an abnormal microenvironment that affects MSC adhesion, migration, proliferation, and differentiation (Padhi and Nain, 2020). For example, in osteoarthritis, the progressive degradation of cartilage ECM significantly alters the microenvironment experienced by resident MSCs (You et al., 2023). The mechanical properties of the ECM, particularly stiffness and topography, also significantly influence MSC fate decisions. Pathological alterations in matrix stiffness, as those occurring in conditions like osteoporosis and osteoarthritis, can shift MSC differentiation preferences, typically promoting adipogenic over osteogenic commitment in low-stiffness environments (Sun et al., 2018). These mechanically induced changes in MSC fate contribute to disease progression by reducing bone formation capacity and increasing marrow adiposity.

3.4 Disease-specific microenvironmental alterations

Since different bone-related pathologies create unique microenvironmental signatures that distinctively influence MSC behavior and fate decisions, understanding these disease-specific alterations is essential for developing targeted therapeutic approaches that address the challenges posed by each condition.

In osteoporosis, the bone marrow microenvironment undergoes significant changes characterized by increased oxidative stress (Riegger et al., 2023), altered cytokine profiles (Zhivodernikov et al., 2023), and modified extracellular matrix properties (Luo et al., 2023). These alterations collectively shift MSC differentiation preference toward adipogenesis at the expense of osteogenesis (Infante and Rodriguez, 2018), contributing to reduced bone formation and increased marrow adiposity (Hoshiba et al., 2012).

The osteoarthritic microenvironment poses a different set of challenges, characterized by abnormal mechanical loading (Fang et al., 2021), chronic low-grade inflammation (Zhang et al., 2020), and progressive cartilage ECM degradation (Kan et al., 2024). These pathological conditions alter the behavior of resident MSCs, impairing their chondrogenic potential and promoting abnormal differentiation patterns that contribute to disease progression. The osteoporotic microenvironment is largely defined by endocrine shifts, specifically estrogen depletion, which disrupts MSC homeostasis (Li et al., 2021). This hormonal decline reconfigures the lncRNA regulatory network, altering how MSCs interpret osteogenic versus adipogenic signals (Li et al., 2024). Furthermore, this imbalance is aggravated by the age-related decline in other systemic hormones, including growth hormone and insulin-like growth factor-1 (Zeng et al., 2024), establishing a metabolic environment that promotes pathological lineage allocation and limits regenerative capacity (Tong et al., 2025).

In bone-related tumors, particularly osteosarcoma, multiple myeloma and leukemia, the microenvironment is characterized by hypoxia (Peppicelli et al., 2025), acidosis (Avnet et al., 2019) and the complex interactions between malignant cells and MSCs. This pathological niche fundamentally alters MSC behavior, often co-opting these cells to support tumor growth and progression (Cortini et al., 2017).

3.5 Metabolic microenvironmental alterations

Beyond inflammatory and hypoxic stresses, metabolic dysregulation constitutes an increasingly recognized feature of pathological bone microenvironments. In conditions such as osteoporosis and osteoarthritis, MSCs transition from oxidative phosphorylation toward aerobic glycolysis (Li et al., 2023), accompanied by the excessive accumulation of reactive oxygen species (ROS) and progressive mitochondrial dysfunction. This metabolic reprogramming is not merely a secondary consequence but it actively drives MSC fate decisions, impairing osteogenic differentiation while promoting senescence and adipogenic lineages (Al-Sammarraie et al., 2024). The resulting ‘mitochondrial compromise’ further diminishes the bioenergetic capacity required for lineage commitment and tissue repair (Li et al., 2017). Consequently, these metabolic

shifts are central to disease progression and therapeutic resistance (Guo et al., 2024), with lncRNAs functioning as key sensors translating oxidative and bioenergetic stress into specific alterations in MSC function (Yan et al., 2023).

4 LncRNAs mediate the interplay between pathological microenvironments and MSC fate

The bidirectional relationship between pathological microenvironments and MSC behavior is frequently mediated by lncRNAs that respond to microenvironmental cues and subsequently regulate MSC fate decisions. This section examines how lncRNAs function at the interface between pathological microenvironments and MSC responses in bone-related diseases.

4.1 Microenvironment-induced changes in lncRNA expression

Pathological microenvironments can significantly alter lncRNA expression profiles in MSCs, subsequently affecting their differentiation potential and functional properties. Below, we discuss the mechanisms by which distinct pathological niches—defined by inflammation, hypoxia, and altered ECM dynamics—induce characteristic lncRNA signatures that drive MSC fate determination.

4.1.1 Inflammatory microenvironment-induced lncRNA alterations

In inflammatory contexts, pro-inflammatory cytokines modulate lncRNA expression patterns in MSCs, potentially contributing to their phenotypic shift from pro-inflammatory to immunosuppressive states as inflammation progresses. A notable example involves the lncRNA HOXA antisense transcript 2 (*HOXA-AS2*), which prevents RELA protein acetylation at lysine 310, thereby inhibiting NF-κB function and relieving its transcriptional repression of osterix (SP7/OSX), ultimately promoting MSC osteogenic differentiation (Zhu et al., 2019). Furthermore, mesenchymal stem/stromal cells from patients with ankylosing spondylitis (ASMSCs) demonstrated a greater capacity for adipogenic differentiation compared to those from healthy donors (HDMSCs). During adipogenesis in ASMSCs, a total of 263 differentially expressed long non-coding RNAs (DE lncRNAs) were identified. Several lncRNAs, including *NR_125386.1*, *NR_046473.1*, and *NR_038937.1*, along with their target genes, were found to be closely associated with the enhanced adipogenesis of ASMSCs. What is more, co-expression analysis revealed significant pairs of differentially expressed lncRNAs and mRNAs (such as *SLC38A5-ENST00000429588.1*, *TMEM61-ENST00000400755.3*, and *C5orf46-ENST00000512300.1*), all of which were implicated in modulating the PPAR signaling pathway, further contributing to the increased adipogenic differentiation of ASMSCs (Cen et al., 2022).

4.1.2 Hypoxic microenvironment-induced lncRNA alterations

Hypoxic conditions, characteristic of many bone pathologies, induce major alterations in lncRNA expression profiles. Under oxygen-deficient conditions, hypoxia-inducible factors activate the transcription of various genes, including lncRNAs, as part of cellular adaptation mechanisms. Within the fracture microenvironment, hypoxia drives the exosomal transfer of lncRNAs, such as *LOC103691165*, from macrophages to BMSCs, thereby promoting osteogenic commitment (Wang et al., 2023). While most research on hypoxia-induced lncRNA expression has focused on cancer cells, similar regulatory patterns likely occur in MSCs exposed to hypoxic microenvironments. Researchers demonstrated 289 differentially expressed lncRNAs between hypoxic and normoxic human placenta-derived MSCs (hP-MSCs). They observed that hypoxic culture conditions promoted the proliferation of hP-MSCs. In addition, hypoxic conditions were found to impact cell cycle progression and activate the PI3K/AKT signaling pathway. Co-expression network analysis of lncRNAs and mRNAs revealed that small nucleolar RNA host gene 16 (*SNHG16*), a lncRNA responsive to hypoxia, is linked to key genes involved in the cell cycle and the PI3K/AKT pathway (Feng et al., 2022).

4.1.3 ECM alteration-induced lncRNA changes

Alterations in extracellular matrix composition and mechanical properties serve as primary triggers for lncRNA dysregulation in MSCs. In osteoarthritic cartilage, ECM degradation has been associated with the upregulation of several regulatory RNAs. For instance, circular RNA-cartilage ECM related (*circRNA-CER*) acts as a sponge for *miR-136* to modulate matrix metalloproteinase 13 (MMP13) expression, thereby accelerating cartilage ECM degradation (Liu et al., 2016). Similarly, lncRNA-cartilage injury related (*lncRNA-CIR*) is selectively upregulated in damaged cartilage ECM; silencing this lncRNA promotes collagen and proteoglycan formation while reducing the expression of matrix-degrading enzymes MMP13 and a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5) (Liu et al., 2014). Moreover, matrix stiffness influences lncRNA expression profiles: the lncRNA H19 imprinted maternally expressed transcript (*H19*) regulates the production of essential extracellular components, including fibrillin-1 and vitronectin. In MSCs derived from osteoporotic patients, *H19* knockdown resulted in a compromised, collagen-poor matrix architecture, which biased MSC fate toward adipogenesis at the expense of osteogenic differentiation and proliferative capacity (Moura et al., 2023).

4.1.4 LncRNA profiles in pathological niches

Distinct bone pathologies create unique microenvironmental stressors that shape lncRNA landscapes and, consequently, MSC fate.

Under osteoporotic conditions, the pathological microenvironment severely compromises MSC osteogenic potential. A transcriptomic profiling of ovariectomized (OVX) mice identified 743 differentially expressed lncRNAs in BMSCs. Co-expression network analysis linked these transcripts to specific differentiation checkpoints, with four candidates validated as primary regulators of BMSC exhaustion in osteoporotic conditions (Gu et al., 2021). Moreover, lncRNAs such as tissue inhibitor of metalloproteinases 3 (*TIMP3*) (Wumiti et al., 2024), regulator of reprogramming (*ROR*) (Fu et al., 2021) and growth arrest-specific 5 (*GAS5*) (Feng et al., 2019) were found to be significantly downregulated in osteoporotic bone, a shift that directly correlates with the loss of osteogenic markers. In osteoarthritis, lncRNAs respond dynamically to mechanical strain. For instance, lncRNA related to mechanical stress (*lncRNA-MSR*) is significantly upregulated in degenerated cartilage subjected to high-intensity mechanical stimulation. This lncRNA drives chondrocyte pathology by sequestering *miR-152* (Liu et al., 2016). Within the tumor microenvironment of bone malignancies, lncRNAs undergo profound reconfiguration. In osteosarcoma, cuproptosis-related lncRNAs have emerged as key prognostic indicators, suggesting their role in modulating the peritumoral niche (Yang et al., 2022). In multiple myeloma, malignant cells utilize exosomal signaling to reprogram this niche; specifically, the lncRNA *RUNX2-AS1* is packaged into exosomes and transferred to MSCs. Once internalized, it forms an RNA duplex with *RUNX2* pre-mRNA, interfering with splicing efficiency and effectively tethering MSCs in a non-osteogenic state (Li et al., 2018).

These altered lncRNA expression profiles correlate with the dysregulated differentiation capacity characteristic of MSCs, highlighting how disease-specific microenvironments can reprogram lncRNA expression to influence MSC fate determination.

4.2 Exosomes as vehicles for lncRNA transfer in microenvironmental communication

Exosomes have emerged as crucial mediators of intercellular communication through their capacity to transfer various bioactive molecules, including lncRNAs, between cells (Kalluri and Lebleu, 2020). In the context of bone-related pathologies, MSC-derived exosomes serve as important vehicles for delivering regulatory lncRNAs to target cells within the microenvironment (Zhu et al., 2022; Wang et al., 2024). Research has demonstrated that osteoblast-derived exosomes regulate osteoclast activity, highlighting the important role of exosomes in bone microenvironment homeostasis and metabolism (Wang et al., 2021; Zhang et al., 2023) . During the osteogenic differentiation of MSCs, lncRNAs function as novel regulatory factors that can be packaged into exosomes and transferred to recipient cells. For example, BMSC-derived exosomes containing

lncRNA metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) enhance osteoblast activity through the *miR-34c*/special AT-rich sequence binding protein 2 (SATB2) axis, improving osteoporotic conditions in experimental models (Yang et al., 2019a). Similarly, the exosomal transfer of lncRNA *H19* from MSCs promotes wound healing by regulating target cell gene expression through competitive binding to *miR-152-3p* (Li et al., 2020). This mechanism represents a sophisticated form of intercellular communication that allows MSCs to influence the behavior of surrounding cells in the microenvironment without direct cell-cell contact.

5 LncRNAs as regulators of MSC fate

Long non-coding RNAs represent a diverse class of RNA transcripts; they exceed 200 nucleotides in length that lack protein-coding capacity but play crucial roles in regulating gene expression and cellular function (Mattick et al., 2023). In recent years, lncRNAs have emerged as important modulators of cell fate determination, influencing numerous aspects of MSC differentiation, maintenance and response to microenvironmental stimuli through diverse molecular mechanisms (Fig.1).

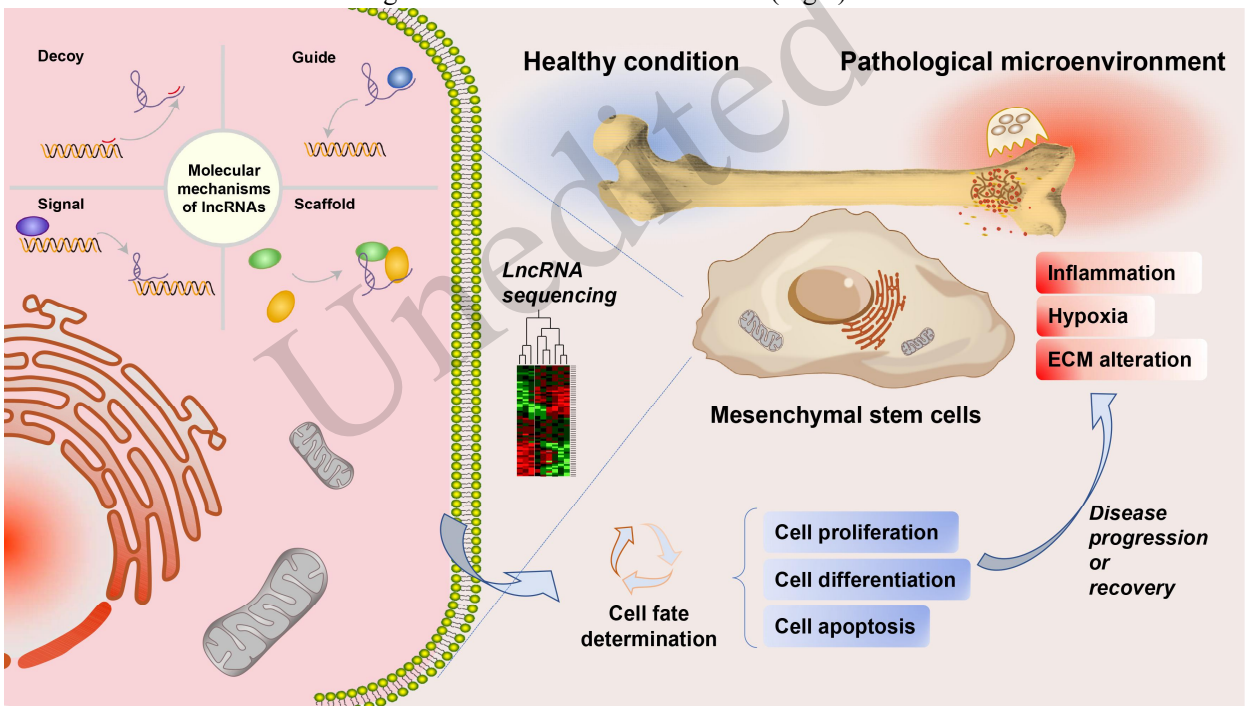

Fig. 1 Influence of Healthy and Pathological Microenvironment on MSC Behavior and Fate Determination
This schematic illustrates how mesenchymal stem/stromal cells (MSCs) are influenced by different microenvironmental conditions. Under healthy conditions, MSCs undergo normal cellular processes, including proliferation, differentiation and apoptosis. However, in pathological microenvironments, characterized by factors such as inflammation, hypoxia and extracellular matrix (ECM) alterations, MSC behavior is significantly altered. LncRNA sequencing can be employed to investigate how MSCs adapt to these conditions, affecting their cell fate determination, which can lead to either disease progression or recovery.

5.1 Classification and molecular mechanisms of lncRNAs

LncRNAs can be classified based on their genomic location relative to protein-coding genes (intergenic, intronic, antisense, etc.), subcellular localization (nuclear, cytoplasmic, or both), or functional properties (Carlevaro-Fita and Johnson, 2019). LncRNAs are involved in diverse molecular mechanisms to regulate gene expression and cellular processes in MSCs. From a functional perspective, lncRNAs can be categorized into four main classes: (1) Due to a predominant mechanism, they function as competing endogenous RNAs

(ceRNAs) or "microRNA sponges," whereby they competitively bind microRNAs and prevent them from targeting their messenger RNA targets. A broad array of lncRNAs, including *ROR* (Fu et al., 2021) and nuclear enriched abundant transcript 1 (*NEAT1*) (Zhang et al., 2019), utilize this strategy to shield critical osteogenic or immunomodulatory transcripts from miRNA-dependent degradation. This competitive interaction allows for the precise titration of downstream signaling outputs, most notably the Wnt/β-catenin and bone morphogenetic protein (BMP) cascades. (2) In another important mechanism involving epigenetic regulation, lncRNAs influence gene expression by recruiting chromatin-modifying complexes to specific genomic loci. Certain lncRNAs serve as scaffolds for these complexes, facilitating their assembly and targeting to particular genes. For example, certain lncRNAs direct histone modifications at promoters of osteogenic master regulators such as OSX, either facilitating or repressing transcriptional accessibility (He et al., 2019). This epigenetic alteration reduces OSX expression and significantly inhibits the osteogenic differentiation of MSCs. (3) LncRNAs also regulate gene expression at the transcriptional level through direct interactions with transcription factors or regulatory elements. These associations allow lncRNAs to modulate the activation threshold of core signaling axes — including the BMP, TGF-β and Wnt pathways— that govern the balance between osteogenic and adipogenic commitment. For instance, lncRNAs have been shown to bind proteins such as members of the heterogeneous nuclear ribonucleoprotein K (hnRNPK) (Tang et al., 2019) or SMAD (Zhang et al., 2019) families, thereby either potentiating or attenuating pathway flux depending on the cellular context. (4) Post-transcriptional regulation represents another important mechanism through which lncRNAs influence MSC fate. In the nucleus, antisense lncRNAs may hybridize with the pre-mRNA of key osteogenic factors (e.g., RUNX2) to interfere with or redirect alternative splicing outcomes (Li et al., 2018). Concurrently, cytoplasmic lncRNAs can dictate the stability of target transcripts by modulating mRNA half-life through direct base-pairing (Li et al., 2019). These post-transcriptional mechanisms provide a versatile regulatory node for the rapid, dynamic reconfiguration of MSC function in response to shifting microenvironmental cues.

5.2 LncRNAs are involved in MSC osteogenic differentiation

Numerous lncRNAs have been identified as critical regulators of MSC osteogenic differentiation, influencing this process through various molecular mechanisms and signaling pathways. High-throughput transcriptomic profiling comparing normal and osteogenically induced human bone marrow-derived MSCs has identified hundreds of lncRNAs with dynamic expression patterns during MSC osteogenic differentiation, reflecting the great breadth of lncRNA-mediated regulation in this lineage (Zhang et al., 2017). To date, elucidated lncRNAs appear to converge on a select group of core signaling hubs and transcriptional effectors. For example, osteogenesis-associated lncRNA (*lncRNA-OG*) promotes BMP signaling through interaction with hnRNPK (Tang et al., 2019), while exosome-shuttled *MALAT1* acts as a molecular decoy for *miR-34c*, effectively de-repressing the essential osteogenic factor SATB2 (Yang et al., 2019b). The lncRNA maternally expressed gene 3 (*MEG3*) plays a crucial role in MSC osteogenic differentiation, particularly in the context of multiple myeloma. Studies have revealed that *MEG3* expression is lower in multiple myeloma MSCs (MM-MSCs) compared to normal donor MSCs during osteogenic differentiation. *MEG3* reduction causes SRY-box transcription factor 2 (SOX2) to dissociate from the BMP4 promoter, disrupting the stable complex formed by *MEG3*, SOX2 and the BMP4 binding region (Zhuang et al., 2015). The reciprocal regulation of osteogenesis and adipogenesis during aging provides a compelling model for lncRNA-mediated fate determination. The bone marrow stem cell–related lncRNA (*Bmncr*) is a definitive example of this dual regulatory role: it scaffolds transcriptional complexes that drive osteogenic programs while simultaneously suppressing adipogenic commitment (Li et al., 2018). These findings illustrate that lncRNAs function as molecular switches that titrate the intensity of lineage-specifying signals. Consequently, their dysregulation directly facilitates the transition toward marrow adiposity and age-related bone loss.

5.3 LncRNAs are involved in MSC immunomodulatory functions

Beyond their roles in differentiation, lncRNAs participate in regulating the immunomodulatory properties

of MSCs, which are critical for their therapeutic applications in inflammatory and immune-mediated disorders. The inflammatory NF-κB pathway plays a central role in regulating MSC immunomodulatory functions, and several lncRNAs have been implicated in modulating this pathway. Specifically, lncRNAs such as *HOXA-AS2* can restrain NF-κB activity by interfering with post-translational modifications of the RelA subunit, thereby preserving osteogenic commitment even under inflammatory duress. This mechanism represents an important link between inflammatory microenvironments and MSC lineage commitment, offering potential therapeutic opportunities for promoting bone formation in inflammatory bone disorders (Zhu et al., 2019). The lncRNA *H19* has been implicated in various biological processes, including glucose and lipid metabolism. It can influence the metabolic state of MSCs, which in turn affects their immunomodulatory capacity, as metabolic reprogramming has been shown to significantly impact MSC immunoregulatory functions. Moreover, the lncRNA *H19* delivered via MSC-derived exosomes has demonstrated significant immunomodulatory effects in wound healing contexts. In diabetic foot ulcer models, *H19* competitively binds to *miR-152-3p*, which normally targets the phosphatase and tensin homolog (*PTEN*) gene (Li et al., 2020). The interplay between MSCs and macrophages, a critical axis in bone healing and remodeling, is also subject to lncRNA regulation. The lncRNA monocyte chemotactic protein 1 regulatory factor (*MRF*), which was identified as a key regulator of monocyte recruitment and macrophage polarization in MSCs cocultured with CD14+ monocytes, influences the chemotactic and immunomodulatory output of MSCs through interactions with RNA-binding proteins, suggesting its potential as a therapeutic target for inflammatory regulation (Lin et al., 2022). This cross-talk between MSCs and macrophages represents an important aspect of tissue repair and regeneration in bone pathologies, with lncRNAs potentially serving as critical mediators of this cellular communication.

6 Therapeutic implications and future perspectives

The complex interplay between pathological microenvironments, MSCs and regulatory lncRNAs offers significant potential for developing novel therapeutic strategies for bone-related diseases. Understanding these intricate relationships provides opportunities for targeted interventions aimed at restoring normal MSC function and promoting tissue regeneration.

6.1 LncRNAs acting as therapeutic targets and biomarkers

The identification of specific lncRNAs involved in MSC fate determination under pathological conditions presents remarkable opportunities for novel therapeutic interventions. First, lncRNAs can serve as valuable biomarkers for disease diagnosis and progression monitoring. The distinct lncRNA expression profiles associated with different bone pathologies might provide diagnostic signatures for early disease detection or assessment of therapeutic efficacy (Patil et al., 2020). Second, the direct modulation of disease-associated lncRNAs offers a potential disease treatment strategy (Coan et al., 2024). For example, in osteoporosis, enhancing lncRNA *MALAT1* expression could potentially improve osteoblast activity through the *miR-34c*/SATB2 axis (Yang et al., 2019b) . Conversely, in multiple myeloma, where lncRNA *HOXC-AS3* impairs osteogenic differentiation via enhancing HOXC10 expression, inhibiting this lncRNA might restore normal MSC function (Li et al., 2019). Furthermore, exosome-based therapies represent another promising approach. MSC-derived exosomes carrying specific lncRNAs may serve as cell-free therapeutic agents with advantages over cellular transplantation, including reduced immunogenicity, enhanced stability and a potential for pharmaceutical standardization (Phinney and Pittenger, 2017; Lotfy et al., 2023). Engineering exosomes to contain particular lncRNAs of interest may enable the targeted delivery of therapeutic molecules to specific cell populations within pathological microenvironments.

6.2 MSC-based therapies in pathological microenvironments

When considering MSC-based therapies for bone-related disorders, the influence of pathological microenvironments on MSC behavior is a critical factor. MSCs transplanted into diseased tissues encounter specific microenvironmental conditions that can significantly affect their therapeutic efficacy (Sui et al., 2019; Redondo et al., 2024). Recent approaches have focused on preconditioning or "priming" MSCs to enhance their resistance to adverse microenvironmental conditions and optimize their therapeutic potential (Sun et al., 2014; Garrido-Pascual et al., 2020; Kahrizi et al., 2023). In fact, various pretreatment strategies, including exposure to inflammatory mediators, hypoxic conditions, three-dimensional culture systems, and diverse chemical or physical stimuli, have been employed to improve MSC paracrine effects (Noronha et al., 2019). While these approaches partially mimic some aspects of disease-specific microenvironments such as inflammation and hypoxia, they often lack the precise pathological signatures characteristic of diseases. Importantly, even when addressing conditions with seemingly similar microenvironmental features, such as wound healing and cancer, MSC-derived therapeutic products may exhibit dramatically different—sometimes opposing—biological effects (Guillamat-Prats, 2021). This observation underscores the need for a more precise characterization of disease-specific microenvironmental attributes and development of correspondingly tailored MSC preconditioning protocols. Therefore, future MSC-based therapeutic approaches should consider both the "spatial" and "temporal" properties of disease microenvironments, recognizing that pathological conditions evolve dynamically over time and exhibit location-specific characteristics that influence MSC responses.

6.3 Challenges and future research directions

Despite the promising potential of lncRNA-based approaches for addressing bone-related pathologies, several challenges and knowledge gaps remain. Firstly, targeting specificity represents a significant hurdle for lncRNA-based therapies; developing effective techniques for specifically manipulating lncRNA expression in desired cell populations without affecting other tissues remains technically challenging. Secondly, understanding the complex regulatory networks involving lncRNAs requires further investigations. To date, most studies have focused on individual lncRNA-target interactions, yet lncRNAs typically function within intricate regulatory networks involving multiple factors. The comprehensive mapping of these networks will provide deeper insights into how lncRNAs coordinate MSC responses to pathological microenvironments and may reveal additional therapeutic opportunities. Thirdly, the dynamic nature of lncRNA expression and function during disease progression necessitates temporal considerations in the therapeutic design. LncRNA roles may evolve throughout different disease stages, requiring time-sensitive intervention strategies. Longitudinal studies tracking lncRNA expression changes during disease development could inform more precisely timed therapeutic approaches. Finally, the integration of multi-omics data should be prioritized to gain comprehensive understanding of lncRNA functions in bone pathologies. Combining genomic, transcriptomic, proteomic, and epigenomic analyses will provide more complete characterization of how lncRNAs regulate MSC fate in pathological contexts and potentially identify novel therapeutic targets or biomarkers.

7 Conclusions

Disease-specific alterations in bone microenvironments create unique signatures that distinctively influence MSC behavior. LncRNAs have been recognized as significant regulators in this intricate process, affecting the differentiation, immune modulation capabilities and reactions of MSCs to microenvironmental signals via various molecular pathways. Understanding these complex relationships provides valuable insights for developing more effective MSC-based therapies that consider the critical influence of pathological microenvironments. Future research should focus on further characterizing the detailed molecular mechanisms through which lncRNAs mediate MSC responses to pathological microenvironments, developing more targeted approaches for lncRNA modulation, and exploring the potential of engineered exosomes containing specific lncRNAs as therapeutic agents. By continuing to elucidate the intricate connections between pathological

microenvironments, MSC fate determination and lncRNA regulation, we can advance our understanding of bone-related disease pathogenesis and develop novel treatment strategies with enhanced efficacy and precision.

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Author contributions

Jingbo LAI contributed to the conceptualization, methodology, and writing of the original draft. Ruolang PAN and Jing ZHENG assisted with data collection, analysis, and literature review. Ye CHEN provided critical insights into the study design and contributed to the revision and final approval of the manuscript. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Jingbo Lai, Ruolang Pan, Jing Zheng and Ye Chen declare that they have no conflicts of interest. This article does not contain any studies with human or animal subjects performed by any of the authors.

Declaration on the use of generative AI tools

No generative AI tools were used in the preparation of this manuscript.

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