Journal of Inflammation Research

Dovepress
Taylor & Francis Group

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REVIEW

Crosstalk Between H-Type Vascular Endothelial Cells and Macrophages: A Potential Regulator of Bone Homeostasis

Jiaxuan Fan, Yaohui Xie, Desun Liu, Rui Cui, Wei Zhang, Mengying Shen, Linzhong Cao

Clinical College of Traditional Chinese Medicine, Gansu University of Chinese Medicine, Lanzhou, People's Republic of China

Correspondence: Linzhong Cao, Clinical College of Traditional Chinese Medicine, Gansu University of Chinese Medicine, Lanzhou, 73000, People's Republic of China, Email 17393118984@163.com

Abstract: The crosstalk between H-type endothelial cells (ECs) and macrophages is critical for maintaining angiogenesis and osteogenesis in bone homeostasis. As core components of type H vessels, ECs respond to various pro-angiogenic signals, forming specialized vascular structures characterized by high expression of platelet-endothelial cell adhesion molecule-1 (CD31) and endothelial mucin (EMCN), thereby facilitating angiogenesis-osteogenesis coupling during bone formation. Macrophages, as key immune cells in the perivascular region, are primarily classified into the classically activated pro-inflammatory M1 phenotype and the selectively activated anti-inflammatory M2 phenotype, thereby performing dual functions in regulating local tissue homeostasis and innate immunity. In recent years, the complex crosstalk between type H vessel ECs and macrophages has garnered significant interest in the context of bone-related diseases. Orderly regulation of angiogenesis and bone immunity provides a new direction for preventing bone metabolic disorders such as osteoporosis and osteoarthritis. However, their interactions in bone homeostasis remain insufficiently understood, with limited clinical data available. This review comprehensively examines the intricate interactions between type H vessel ECs and macrophages with diverse phenotypes, and Insights into the signaling pathways that regulate their crosstalk, focusing on their roles in angiogenesis and osteogenesis. Furthermore, the review discusses recent interventions targeting this crosstalk and the challenges that remain. These insights may offer new perspectives on bone homeostasis and provide a theoretical foundation for developing novel therapeutic strategies.

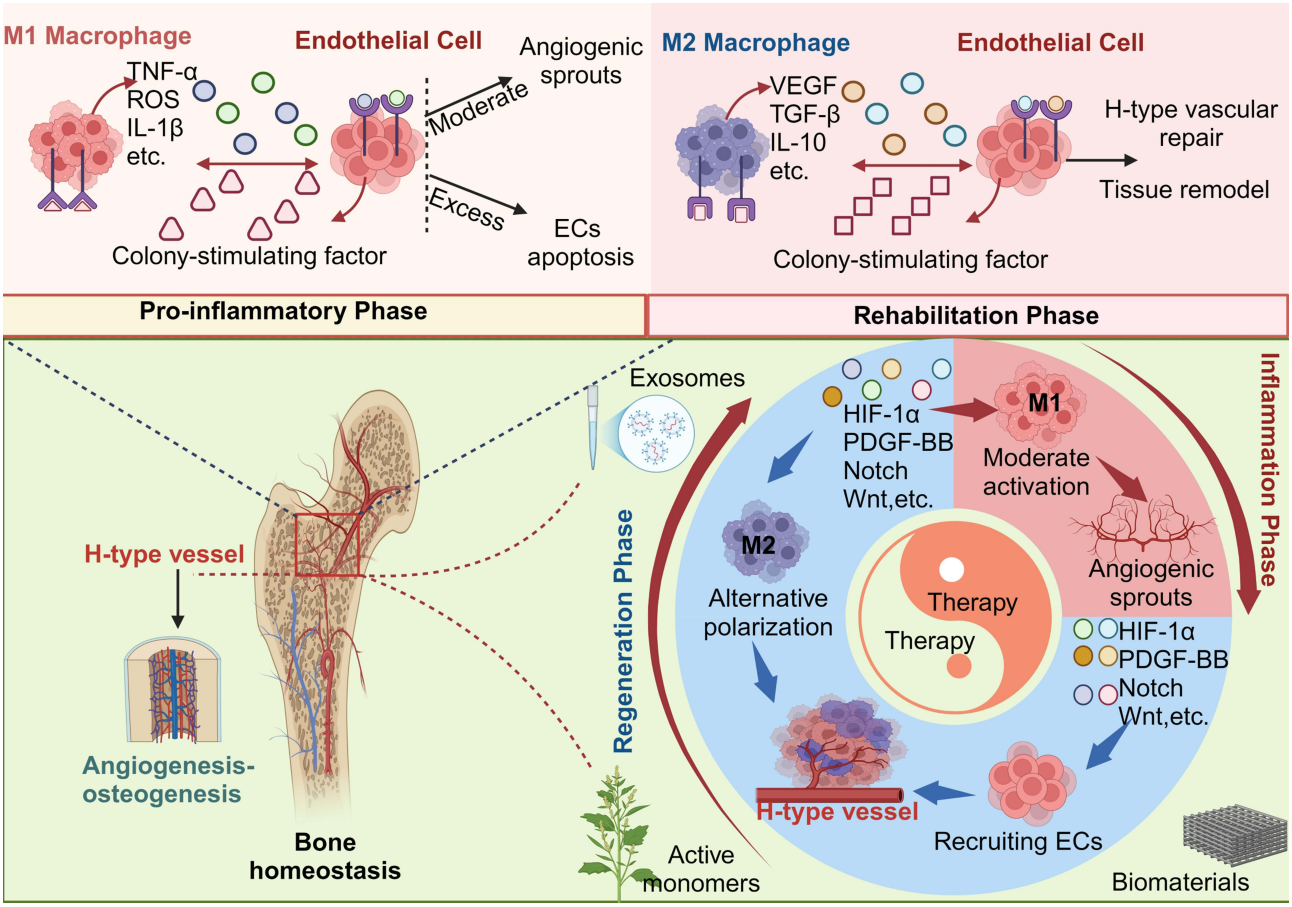
Keywords: H-type vascular, endothelial cells, macrophages, molecular crosstalk, angiogenic-osteogenic coupling, bone homeostasis, interventions

Introduction

Bone homeostasis is regulated by the dynamic balance between bone formation and resorption, and its disruption is a primary cause of metabolic bone diseases such as osteoporosis (OP) and osteoarthritis (OA).[1,2] Type H vessels, characterized by high expression of platelet endothelial cell adhesion molecule-1 (CD31) and endothelial mucin (EMCN), support angiogenesis-osteogenesis coupling and supply essential oxygen and nutrients to cells in the metaphysis, thus maintaining bone homeostasis.[3] As critical cells for repairing type H vessels and supporting bone homeostasis, endothelial cells (ECs) respond to signaling pathways, including hypoxia inducible factor-1α (HIF-1α)/vascular endothelial growth factor (VEGF), Notch, platelet-derived growth factor-BB (PDGF-BB), and Wnt/glycogen synthase kinase 3β (GSK3β), to promote angio-genesis-osteogenesis coupling.[4,5] Perivascular macrophages surrounding type H vessels sense microenvironmental stimuli, regulate immune responses, and contribute to bone tissue repair.[6] They primarily differentiate into classically activated M1 and alternatively activated M2 phenotypes, and the conversion between these pro-inflammatory M1 and anti-inflammatory M2 subtypes in specific environments facilitates their dual roles in inflammatory responses.[7] During vascular repair, macrophages promote EC migration, recruitment, proliferation, and differentiation by degrading the extracellular matrix (ECM) and releasing pro-angiogenic factors, such as VEGF,

Received: 23 October 2024
Accepted: 30 January 2025
Published: 25 February 2025

Graphical Abstract



vascular cell adhesion molecule 1 (VCAM1), and von Willebrand factor (vWF).[8,9] Meanwhile, ECs modulate macrophage colony-stimulating factor (M-CSF) signaling to promote selective macrophage growth and differentiation.[10] Highlighting the reciprocal crosstalk that enhances type H vessel network formation.

With recent advances in osteoimmunology, the crosstalk between type H vessel ECs and macrophages regulates bone homeostasis by shaping the bone immune microenvironment. Under conditions of local ischemia, hypoxia, or pathogen-induced injury, type H vessel ECs at the injury site form the foundation for constructing new vascular scaffolds and interact with macrophages to selectively migrate to injured or infected areas. Through self-renewal and signal reception, they recruit bone marrow mesenchymal stem cells (BMSCs) and osteoblasts (OBs) to the injured bone tissue, promoting angiogenesis-osteogenesis differentiation and improving bone homeostasis.[11,12] Furthermore, exosomes, natural bioactive components, and novel materials that mediate type H vessel EC-macrophage crosstalk show unique advantages in facilitating angiogenesis-osteogenesis coupling. However, mechanistic studies are still in their early stages. In-depth investigation of preventive strategies targeting ECs-macrophages crosstalk will help reveal the underlying molecular mechanisms and provide strategies for regulating bone homeostasis to prevent and treat metabolic bone diseases.

H-Type Vascular and Bone Homeostasis

Bone microvasculature is a critical component of the bone microenvironment, fulfilling the metabolic demands of various bone cells and promoting bone repair through the secretion of multiple cytokines.[13] Based on differential expression patterns of CD31 and EMCN in ECs, Kusumbe first classified micro-vessels into type H (CD31^hiEMCN^hi) and type

L (CD31^loEMCN^lo) vessels. This classification reflects the progression from the disruption of the primitive vascular basement membrane and EC migration/proliferation to the differentiation of ECs into distinct microvascular subtypes (H and L) under varying concentrations of endothelial factors regulated by HIF-1α/VEGF, Notch, and PDGF-BB signaling pathways, ultimately promoting the formation of an integrated vascular network.[14,15] Type H vessels predominantly localize near the growth plate in metaphyseal and trabecular bone regions, providing an optimal microenvironment for nearby cells and recruiting osteoprogenitors to injured sites. This process leads to the upregulation of runt-related transcription factor 2 ($Runx2^+$) and $Osterix^+$ cells, thereby facilitating significant osteogenic coupling.[16,17] In contrast, type L vessels primarily localize in the diaphyseal region, with minimal recruitment of surrounding osteogenic cells.[18] Studies indicate that type H vessels are most prevalent in young growing mammals near the growth plate, with their abundance declining with age, accompanied by a marked decrease in surrounding osteoprogenitor numbers.[19] Simultaneously, type H vessels in bone mineralization zones show time-dependent proportional decreases, while their abundance notably increases in adjacent or pre-mineralized regions.[20] Additionally, inducing H-type angiogenesis effectively stimulates osteogenesis in the avascular condylar regions of patients with limited growth potential,[21] highlighting their crucial role in maintaining bone homeostasis.

The "neovascularization-OB-osteoclast (OC)" tripartite regulatory mechanism reflects the key process by which type H vessels regulate bone homeostasis. As an upstream driver of bone formation, type H vessel ECs recruit OB and OC progenitors to injured sites through paracrine signaling molecules, including bone morphogenetic protein (BMP), osteoprotegerin (OPG), and type I collagen α1 (COL1A1).[22] These ECs provide essential nutrients, oxygen, multipotent cells, and minerals, leading to high expression of osteogenic factors such as osteocalcin (OCN) and alkaline phosphatase (ALP), thereby providing scaffolds and stable pathways for bone cells. This supports the metabolic requirements and related mRNA expression of osteoprogenitors, OBs, and OCs within bone defects, promoting bone formation.[23] In mouse femoral defect models, type H vessel ECs up-regulate HIF-1α to counter oxidative stress, enhancing bone density and remodeling.[24] Simultaneously, the upregulation of HIF-1α promotes H-type angiogenesis and the recruitment of $Osterix^+$ cells, enhancing vascularized bone formation in mandibular defects.[25] Conversely, specific knockout of HIF-1α and BMP4 in ECs leads to suppressed BMSC osteogenic differentiation.[26] At the same time, bone cells secrete VEGF, VCAM1, angiopoietin-1 (Ang1), and basic fibroblast growth factor (bFGF) to promote type H vessel formation, establishing a positive feedback loop[27,28] (Figure 1).

Macrophage Polarization in Angiogenesis

Macrophages originate from monocytes, which differentiate from hematopoietic stem cell-derived intermediate progenitors in the bone marrow. As crucial components of the innate immune system, they perform diverse functions in skeletal and muscular inflammation, including the clearance of invading pathogens, phagocytosis of apoptotic cells, and promotion of antigen presentation to activate the immune system.[29,30] Due to their high plasticity and heterogeneity, macrophages can exhibit different phenotypes (M1, M2) to mount appropriate responses to pathogens or signaling molecules.[31] Their polarization into inflammatory M1 or anti-inflammatory M2 phenotypes is regulated by factors such as epigenetics, metabolic reprogramming, and mechanical stimulation, responding to tissue microenvironments to participate in angiogenesis.[7]

Epigenetic Regulation

Epigenetic processes include DNA methylation, histone modifications, and chromatin remodeling.[32] Pro-inflammatory gene expression and DNA methyltransferase (DNMT) expression correlate with M1 macrophage polarization. Research has shown that Interleukin-4 (IL-4) and IL-13 activated epigenetic and transcriptional programs selectively induce M1 macrophage polarization under hypoxic conditions, leading to an imbalance in the VEGFA-VEGFR1 axis and suppressed angiogenic activity.[33] In ovariectomized mouse models, DNMT inhibitors counteract macrophage DNA methylation, downregulating IL-6 and tumor necrosis factor alpha (TNF-α) levels while promoting cell proliferation and angiogenesis.[34] Histone deacetylases (HDACs) are key proteins in epigenetic modification. In high-glucose or lipopolysaccharides (LPS)-enriched environments, elevated HDAC6 and IL-1β expression levels suppress IL-10 production, promote M1 macrophage polarization, and impair angiogenesis and wound healing in mice.[35] Conversely, inhibiting HDAC3 expression downregulates IL-1β, IL-6, and TNF-α levels in macrophages, while upregulating arginase 1 (Arg1)

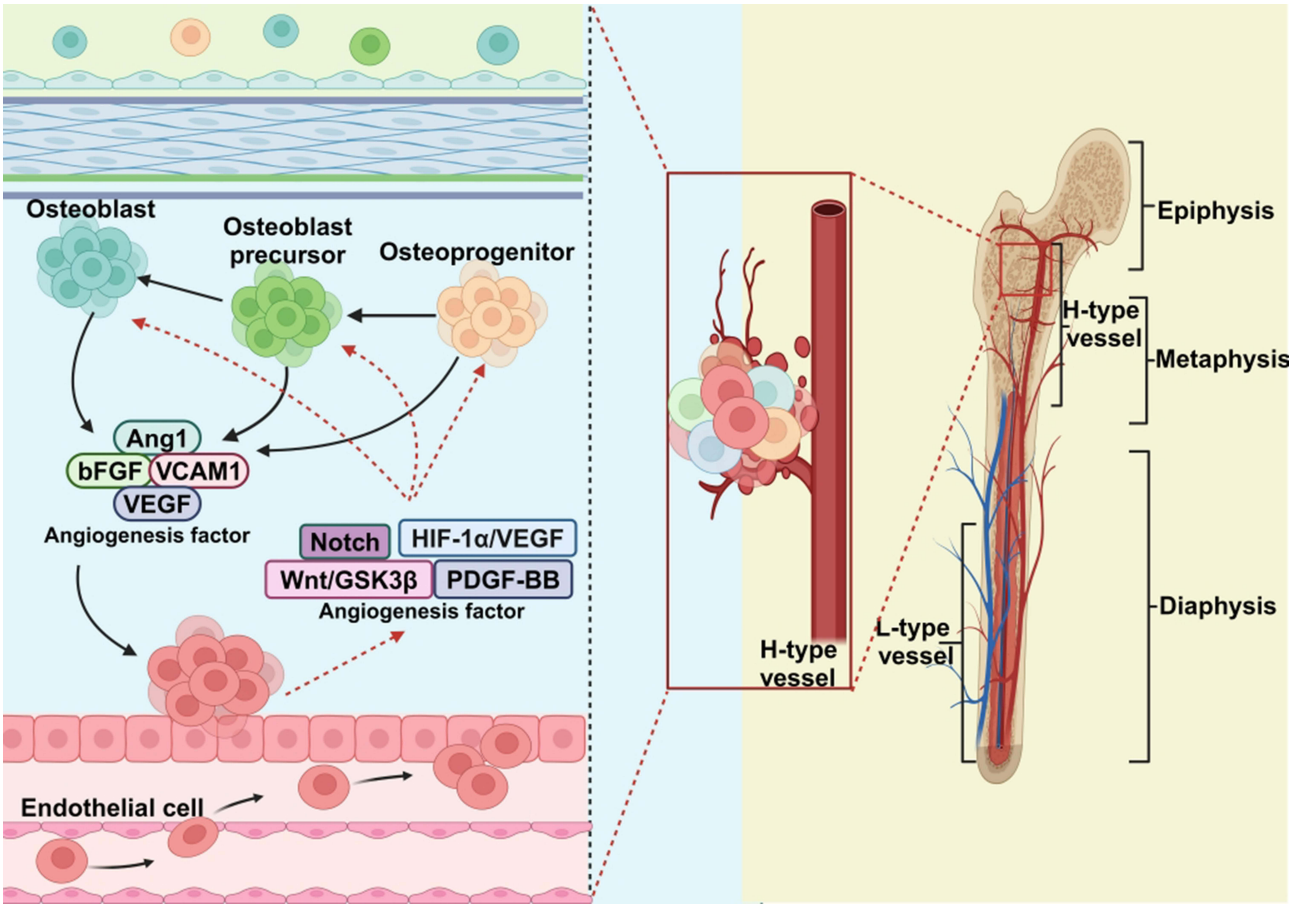


Figure 1 H-type Blood Vessels in Bone Remodeling. During tissue repair and remodeling, ECs promote the proliferation and differentiation of osteoprogenitor cells and osteoblasts by activating key signaling pathways, including HIF-1α/VEGF, Notch, PDGF-BB, and Wnt-GSK3β. Simultaneously, osteoprogenitor cells and osteoblasts secrete several factors, such as VEGF, VCAM1, Ang1, and bFGF, which stimulate the migration and recruitment of ECs in H-type blood vessels, thereby facilitating the coupling of angiogenesis and osteo-genesis. H-type blood vessels are primarily located in the metaphysis and periosteal regions of bone, whereas L-type blood vessels are predominantly found in the diaphysis. These two vascular networks converge at the metaphyseal-diaphyseal junction, forming a unified vascular network that delivers oxygen and nutrients to bone cells, thereby promoting bone regeneration.

expression to promote M2 polarization, counteracting oxidative stress-induced angiogenesis inhibition.[36] Similarly, HDAC4 and HDAC5, in association with overexpressed m6A demethylase 3, negatively regulate M2 macrophages and suppress vascular repair.[37] Furthermore, the therapeutic potential of targeting microRNAs to regulate macrophage polarization in angiogenesis has gained attention. In peripheral blood circulation, miR-17-20a enrichment drives M2 polarization, upregulating VEGF levels to promote angiogenesis and restore perfusion balance and vascular reconstruction.[38] High expression of microRNA-155-5p pro-motes M1 macrophage polarization, inhibiting EC activity and angiogenic capacity while slowing wound healing.[39]

Metabolic Regulation

Metabolic reprogramming influences macrophage polarization and has clear effects on vascular repair. M1 macrophages depend on glycolysis, while M2 macrophages use oxidative phosphorylation and the TCA cycle for polarization.[7,40] Excessive reactive oxygen species (ROS) accumulation leads to mitochondrial dysfunction in macrophages, promoting glycolysis, driving M1 macrophage polarization, upregulating pro-inflammatory factors such as nuclear factor kappa-B (NF-κB) and TNF-α around ECs, and inhibiting vascular reconstruction.[41] Effective ROS elimination suppresses oxidative stress, restores mitochondrial oxidative phosphorylation, and promotes vascular repair and regeneration.[42] Simultaneously, targeted inhibition of glycolysis can upregulate Arg1 expression, increase the differentiation of pro-

regenerative $CD206^+$ M2 macrophages, and enhance angiogenesis and bone remodeling through targeted immune metabolism.[43]

Lipid metabolism characterizes the selective macrophage polarization process, where fatty acid (FA) synthesis and uptake promote M1 macrophage expression, while FA oxidation tends to drive M2 polarization. Substantial FA accumulation induces M2 to M1 macrophage transformation, enhancing oxidative stress, inflammatory damage, and pathological angiogenesis.[44] Lipoprotein lipase, as an FA uptake gene, mediates low-density lipoprotein accumulation in monocytes, inducing IL-1β and TNF-α expression, and promoting M1 polarization. Activating peroxisome proliferator-activated receptor and peroxisome proliferator-activated receptor gamma coactivator 1β expression can promote lipid metabolism to induce M2 polarization.[45] Additionally, a short-term high-fat diet upregulates triglyceride lipase activity, facilitates triglyceride hydrolysis, stimulates M2 macrophage infiltration, and benefits vascular repair at the defect site.[46]

Amino acid metabolism regulates macrophage polarization depending on its metabolic pathways. Argi-nine activates the inducible nitric oxide synthase pathway to generate NO, promoting M1 macrophage polarization, while targeting Arg1 metabolism can promote M2 infiltration and vascular tissue repair.[47] High glutamine metabolism promotes M2 macrophage polarization and angiogenesis,[48] and it can also support the tricarboxylic acid cycle to enhance executive effects.[49] Autophagy, as an important metabolic pathway for macrophages, accompanies protein homeostasis reconstruction and mediates CD68, Arg1, and autophagy-related gene autophagy related 16 Like 1 expression to reprogram macrophage polarization. High autophagy flux drives M2 conversion, while autophagy damage leads to upregulated IL-6 and TNF-α expression, promoting M1 polarization and severely disrupting vascular generation.[50]

Moreover, acid-base metabolic balance provides a physicochemical environment for macrophage polarization. An alkaline environment (pH 8.2) promotes the release of IL-1β, TNF-α, and other factors, stimulating macrophages toward M1 polarization, whereas an acidic environment (pH 6.6) upregulates Arg1 and CD206 levels, inducing a tendency towards M2 conversion. Interestingly, an early local alkaline microenvironment is more conducive to promoting EC proliferation, migration, and vessel budding.[51]

Mechanical Stimulation

Mechanical stimulation from the peripheral environment promotes macrophage polarization, providing an important strategy for vascular regeneration. Macrophages respond to compression and stretching strain to repair damaged tissue. Mechanical stretching promotes the release of IL-10 and transforming growth factor-β (TGF-β) to stimulate M2 macrophage polarization, while stress tends to drive M1 polarization.[52] Early static compression increases IL-6, TNF-β, and chemokine IL-8 release, reversing local hypoxic damage, upregulating VEGFA expression, and promoting angiogenesis.[53] Additionally, mechanical support is beneficial for enhancing ROS clearance capacity, driving M2 macrophage polarization, promoting anti-inflammatory IL-10 and healing factors such as VEGF and bFGF expression, improving the in situ regenerative microenvironment, and synergistically accelerating vascular regeneration.[54]

In summary, the dynamic balance of macrophage polarization is crucial for maintaining immune homeostasis (Figure 2). Inducing earlier and more abundant M2 macrophage infiltration will provide potential targets for vascular repair. Multi-omics analysis of macrophage polarization, including transcriptomics and metabolomics, provides a basis for treatment strategies in angiogenesis. However, the diversity of macrophages makes the M1/M2 binary classification difficult to guide clinical diagnosis and treatment. Therefore, it is essential to deeply analyze the characteristics and functional heterogeneity of macrophages. A recent study that spatially analyzed macrophage populations in different human tissues revealed a complex spatial tissue network consisting of five distinct macrophage populations existing in isolated microenvironmental niches,[55] which may provide a new perspective on the complex phenotypic heterogeneity of macrophages.

H-Type Endothelial Cell-Macrophage Crosstalk Mechanism

Macrophages play a pivotal role in bone repair by facilitating angiogenesis and osteogenesis through the degradation of ECM components and the release of angiogenic factors, including bFGF, PDGF, macrophage inflammatory protein-1 (MIP-1), These factors guide the migration of ECs to the injury site, thereby promoting H-type angiogenesis-osteogenesis coupling.[8,56] In the early phase of bone healing, pro-inflammatory M1 macrophages dominate, followed by anti-inflammatory M2 macrophages driving healing. Moreover, direct interactions between H-type ECs and macrophages,

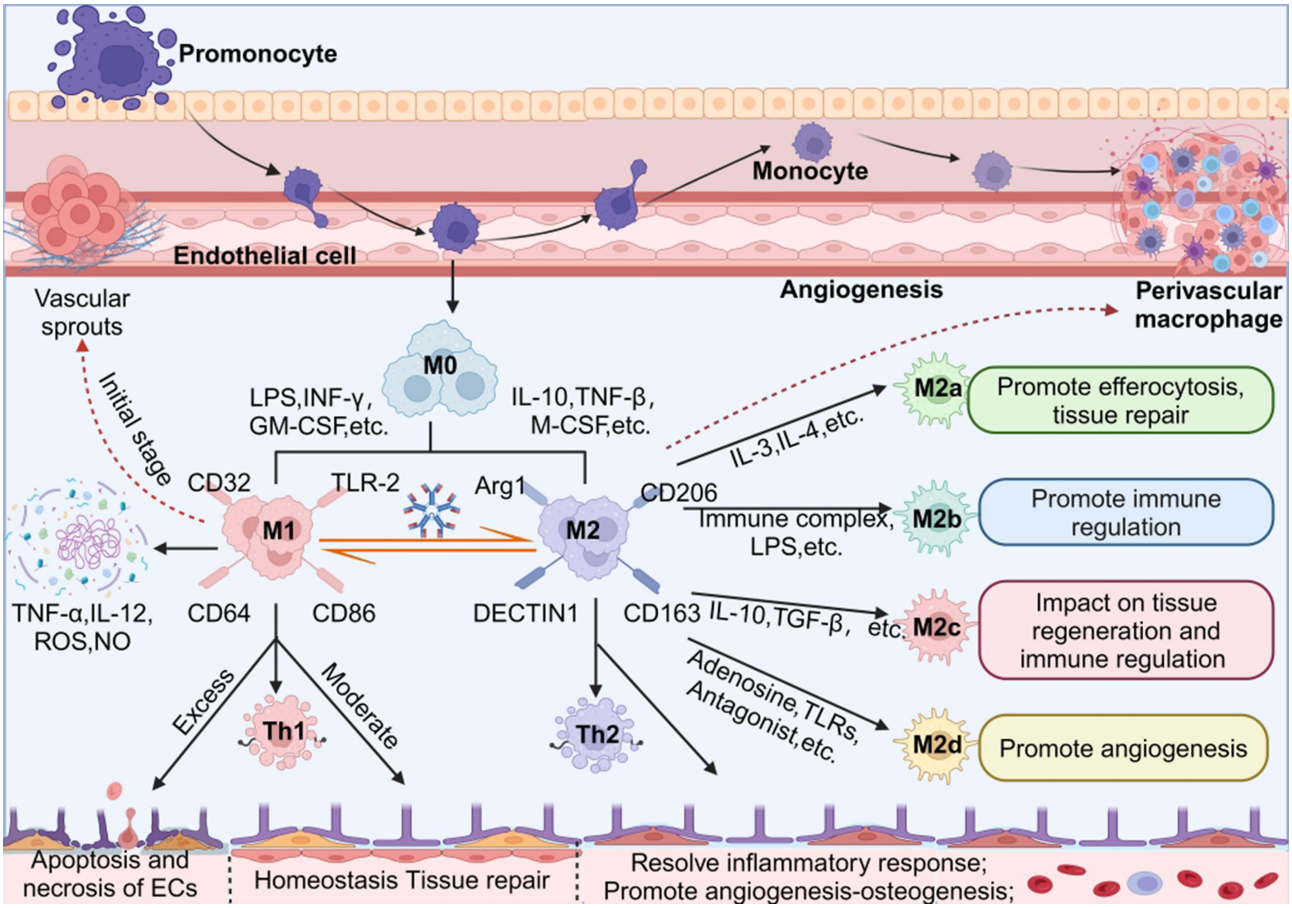


Figure 2 Macrophage Polarization and Its Role in Angiogenesis. Monocytes differentiate into macrophages, which then polarize into M1 or M2 phenotypes to respond appropriately to pathogens or signaling molecules. M1 macrophages express surface markers such as CD32, CD64, CD86, and TLR-2, and are activated early in inflammation by factors such as LPS, interleukins (IL-1, IL-2, IL-6, IL-8, etc.), interferon-gamma, and GM-CSF. These cells release pro-inflammatory cytokines (TNF-α, IL-12, nitric oxide) and ROS, driving Th1 immune responses. Early M1 activation can stimulate angiogenesis, and moderate infiltration supports tissue repair. However, excessive M1 activation leads to leukocyte infiltration, EC apoptosis, and necrosis. M2 macrophages, characterized by markers such as CD163, CD206, Arg1, and dendritic cell-associated C-type lectin 1, represent an alternative activation phenotype. These macrophages are activated later in the inflammatory process or in anti-inflammatory environments by cytokines like IL-4 and IL-10. M2 macrophages promote Th2 immune responses by secreting anti-inflammatory cytokines (IL-10, TGF-β, VEGF), thereby supporting humoral immunity, tissue repair, angiogenesis, and the suppression of inflammation. Based on differences in stimuli and functions, M2 macrophages are further classified into subtypes: M2a (activated by IL-4, IL-13), M2b (activated by immune complexes, LPS), M2c (activated by IL-10, TGF-β, glucocorticoids), and M2d (activated by TLR antagonists, adenosine). M2a promotes phagocytosis and tissue repair, M2b regulates immune responses, M2c enhances IL-10 expression, affecting tissue regeneration and immune regulation, while M2d supports angiogenesis.

through the paracrine release of Wnt, CXC chemokine ligand 14, and lysyl oxidase, regulate M-CSF signaling pathways to selectively promote macrophage growth and polarization, particularly toward the M2 phenotype. This polarization not only facilitates macrophage recruitment but also fine-tunes the bone immune microenvironment.[57,58] Consequently, the interaction between ECs and macrophages enhances angio-genesis.

HIF-1α/VEGF

The HIF-1α/VEGF signaling axis plays a crucial role in cellular responses to hypoxia, particularly in the context of H-type EC-macrophage interactions. Under hypoxia, HIF-1α accumulates in the nucleus, forming a heterodimer with HIF-1β. This complex binds to hypoxia response elements in DNA, upregulating VEGF expression, which then engages cell surface receptor tyrosine kinases to stimulate EC migration, recruitment, and vessel fusion.[5,13,59] Subsequently promotes the stability and maturation of H-type vessels, along with an increase in Osterix^{+} cells, thereby targeting the induction of angiogenesis-osteogenesis differentiation.[60] Simultaneously, the release of HIF-1α and VEGF induces the migration of monocytes, which differentiate into M1 macrophages that infiltrate the injury site and initiate vascular sprouting. Over time, macrophages respond to the hypoxic microenvironment, particularly to IL-4 and IL-10, polarizing

to the M2 phenotype, upregulating IL-1β and endothelial nitric oxide synthase (eNOS) levels, and further enhancing VEGFA and bFGF expression, thereby recruiting additional macrophages to promote angiogenesis. Furthermore, vascular sprouting in the hypoxic niche activates EC migration to intensify the angiogenic response.[61,62] Studies indicate that in a rat skeletal muscle contusion model, hyperbaric oxygen therapy inhibits HIF-1α prolyl hydroxylase expression, activating the HIF-1α/VEGF pathway and stimulating EC and macrophage proliferation, which accelerates H-type vascular formation.[63] During the first phase of bone healing (the post-inflammatory phase), HIF-1α/VEGF activation helps counteract hypoxia near the growth plate, recruiting ECs and M1 macrophages to the injury site, co-regulating VEGFA expression, and initiating vascular sprouting into the hypoxic region. In the subsequent phase (woven bone formation), upregulation of the macrophage marker CD206 strongly drives M2 polarization, promoting EC proliferation and remodeling of the H-type vascular network.[64] Furthermore, in a mouse arterial excision model, stem cell-derived smooth muscle cells induced M2 macrophage polarization, enhancing the recruitment of ECs and promoting the HIF-1α/VEGF axis, which supported H-type vessel formation.[57] IL-19 upregulates VEGFA mRNA in ischemic environments, promoting EC and M2 macrophage polarization to enhance angiogenesis.[65] Additionally, HIF-1α reduces macrophage glycolytic activity by limiting glucose uptake, inhibiting granulocyte-macrophage colony-stimulating factor (GM-CSF) induced fusion of $CD14^+$ monocyte precursors, thereby fostering vessel-osteogenesis coupling.[66]

PDGF-BB

PDGF-BB, primarily secreted by OC precursors in bone, acts as both a chemoattractant and mitogen, interacting with PDGFβ receptors to stimulate the migration and recruitment of endothelial progenitor cells (EPCs) and BMSCs, activating mitogen-activated protein kinase signaling pathways and promoting H-type vessel formation at the injury site.[3,67] Additionally, PDGF-BB is released by $CD206^+$ M2a macrophages, which, upon hypoxic stimulation, transform into pericyte-like cells, secreting angiogenesis-promoting factors such as PDGF-BB and VEGF to induce EC differentiation into tip cells, thereby stimulating vessel sprouting. PDGF-BB further promotes the recruitment of additional pericytes, facilitating the maturation of H-type vessels.[68,69] Studies in mouse tibial injury models demonstrate that mitochondrial oxidative stress induces M2a macrophage polarization, activating PDGF-BB signaling to restore EPC function and promote EC and macrophage proliferation, thereby supporting H-type vascular remodeling and bone repair.[70] In a mouse femoral defect model, local upregulation of PDGF-BB expression improved LPS-induced inflammation, inhibited the mRNA expression of IL-6, IL-17a, and TNF-α, and increased IL-10 release, which drove M2 macrophage polarization and recruited differentiated ECs, resulting in H-type vessel-osteogenesis coupling.[71] Moreover, lactate accumulation from glycolysis enhances the effects of LPS, leading to more pronounced PDGF-BB expression.[72] In a rabbit tibial defect model, high PDGF-BB expression upregulated IL-10 and Arg1, driving M2 polarization and EC proliferation, which further stimulated H-type vessel formation and stabilized the pericyte environment.[73] In an ovariectomized (OVX) mouse model, PDGF-BB enhanced M-CSF-induced macrophage differentiation in a dose-dependent manner, promoting angiogenesis factor expression and EPC migration, which facilitated H-type vessel formation.[74]

Notch

The Notch signaling pathway is a highly conserved system composed of ligands (Delta-like (DLL) 1, Dll4, Jagged1, Jagged2) and Notch receptors (Notch1-4). It functions through ligand-receptor binding and proteolysis, releasing the Notch intracellular domain (NICD) into the cell nucleus to activate target gene transcription.[14,16] Notch signaling activity is regulated by local blood circulation, where the small diameter and high flow velocity of H-type vessels stimulate Notch signaling. This, in turn, promotes the secretion of morphogenic protein antagonists and VEGF, upregulating the number of EPCs and osteoprogenitor cells in necrotic areas.[5] VEGF subsequently enhances the expression of Dll4, which further stimulates NICD release in neighboring ECs, activating ligand/receptor binding and forming a feedback loop that promotes H-type angiogenesis.[13] Conversely, silencing DLL4/Notch pathway inhibits H-type vessel maturation, reduces the recruitment of $Runx2^+$ osteoprogenitor cells, leads to femoral defects and impairs mandibular bone quality.[75] Additionally, ECs regulate Notch signaling to control the differentiation and maturation of recruited monocytes into macrophages, playing a role in vascular homeostasis and cellular immunity, which further promotes H-type angiogenesis and bone repair.[76] When NICD enters the nucleus and binds to recombination signal-binding protein-J (RBP-J), it exerts immune effects, and it is

generally considered that Notch expression is associated with M1 polarization.[77,78] Resting macrophages express all four Notch receptors, while activated macrophages selectively upregulate Notch1 levels.[79] Studies have shown that downstream mediators of Notch signaling, such as miR-125a, can inhibit the expression of HIF-1α and interferon 4, driving M1 polarization.[80] Conversely, increased eNOS expression activates the HIF-1α/Notch1 signaling pathway, inducing M2 macrophage conversion and exhibiting effective anti-inflammatory activity.[81] In hypoxic environments, Dll1 protein levels in ECs are upregulated, stimulating RBP-J expression to promote Notch signaling. This, in turn, induces macrophage differentiation and maturation, upregulating VEGFA expression to improve EC proliferation, differentiation, and angiogenesis.[82] In a mouse model of peripheral limb ischemia, colony stimulating factor 1 (CSF1), as an ischemic niche factor, binds non-redundantly with the Dll1 gene, promoting glycolysis and macrophage reprogramming, thereby restoring ischemic perfusion and bone tissue repair.[83] Furthermore, in a mouse femur injury model, Notch signaling promotes M1 polarization, enhancing early vascular nutritional support, while Jagged1 and Notch overexpression stimulate EC sprouting and longitudinal vascular growth.[84] This suggests that Notch signaling acts as a crosstalk mechanism between macrophages and ECs to enhance the stability and maturity of H-type vascular sprouts.

Wnt-GSK3β/β-Catenin

Wnt proteins activate the Wnt-GSK3β/β-catenin pathway by binding to frizzled receptors, inhibiting GSK-3β expression. This results in the translocation of non-phosphorylated β-catenin to the nucleus, where it coordinates the expression of growth factors such as VEGF and TGF, facilitating the proliferation and renewal of BMSCs and ECs.[5,14,16] GSK3β, an inhibitor of the Wnt pathway and a key node in EC converging signaling, is inactivated under hypoxic conditions, promoting the expression of HIF-1α, which targets VEGF and Ang1 to promote angiogenesis. Simultaneously, silencing GSK3β expression induces β-catenin translocation to the nucleus, activating TGF transcription and improving H-type angiogenesis.[85] In ECs, kinase-mutated forms of enzymes increase intracellular β-catenin levels, promoting VEGF receptor phosphorylation and upregulating VEGF expression, thereby indirectly participating in vessel-bone coupling.[86] Wnt/β-catenin signaling mediates the conversion of M1 to M2 macrophages, exerting anti-inflammatory effects. During bone repair, Wnt/β-catenin signaling drives macrophages to polarize to the M2 phenotype via paracrine signaling in the inflammatory microenvironment, upregulating the expression of Arg1, VEGF, BMP2, and other factors, thereby stimulating EC proliferation and differentiation to activate vascular remodeling and bone regeneration.[87] In an OVX rat model, GSK3β and NF-κB signaling pathways synergistically shape the inflammatory environment, promoting M1 macrophage polarization, suppressing PDGF-BB gene expression, and impairing H-type vascular remodeling near the growth plate.[74] In contrast, in a femoral defect model, Wnt/β-catenin signaling enhances the stability of Wnt9a and β-catenin in macrophages, inhibits NF-κB nuclear translocation, downregulates IL-6 and TNF-α to suppress M1 infiltration, and promotes the expression of IL-8, VCAM1, and vWF in ECs, enhancing anti-inflammatory and angiogenic effects.[88] Furthermore, activating Wnt/β-catenin signaling leads to the transcriptional deactivation of M1 macrophage DNA, suppressing their epigenetic modification while upregulating the expression of vWF, VEGF, and matrix metalloproteinases (MMPs), stimulating EC proliferation and promoting vascularized bone formation.[89] This demonstrates the crosstalk between the Wnt-GSK3β/β-catenin pathway in macrophages and ECs to achieve vessel-bone coupling.

Integrin

Integrins are transmembrane proteins composed of α and β subunits that are highly expressed during angiogenesis. They transmit extracellular signals by interacting with the ECM and promote the degradation of ECM components. This signaling cascade fosters the accumulation of ECs and helps maintain the stability of H-type vessels. Mice deficient in integrin β1 exhibit defects in EC differentiation, resulting in a significant reduction in the abundance of H-type vessels.[90] Integrins α1β1 and α2β1 are upregulated during VEGF-induced angiogenesis, stabilizing HIF-1α and promoting vessel formation. Moreover, COL1A1 can induce the reorganization of integrin α2β1 in ECs, enhancing angiogenic activity.[91] The specific type of integrin subunits plays a decisive role in the phenotype and function of macrophages. During bone healing, integrin β1 binds to fibronectin on the surface of bone implants, promoting the expression of M2 macrophage markers such as CD163 and CD206. In contrast, integrin β2, by activating downstream NF-κB phosphorylation, tends to induce M1 macrophage polarization.[92] Additionally, integrin α1 derived from ECs promotes the uptake of CSF1 by

macrophages, which helps maintain macrophage homeostasis.[93] These findings suggest that integrins are essential mediators of crosstalk between ECs and macrophages. Under hypoxic-ischemic conditions, activation of integrin αVβ1 in ECs induces the paracrine secretion of HIF-1α, VEGFA, and other factors, promoting EC proliferation and differentiation while inhibiting M1 macrophage infiltration.[94,95] In inflammatory environments, the activation of integrin α2β1 receptors inhibits the expression of IL-17, NF-κB, and other inflammatory markers, driving macrophages toward M2 polarization, which results in the release of Arg1 and CD206 proteins. This creates a favorable immune microenvironment for H-type angiogenesis, which further upregulates VEGF levels in ECs, thereby enhancing the synergistic effects of immune regulation and vascularized bone formation.[96]

Other Potential Signaling Pathways

Transforming TGF-β is a critical factor secreted by macrophages that stabilizes the H-type vascular system. In bone repair, TGF-β1 activation inhibits NF-κB expression, driving anti-inflammatory M2 polarization, upregulates VEGFA mRNA levels, and promotes H-type vessel-bone coupling.[97,98] OPG, primarily secreted by ECs in the vascular microenvironment, competes with receptor activator of nuclear factor-κ B ligand (RANKL) to inhibit IL-6 expression, promote M1 to M2 macrophage conversion, and increase VEGF levels, thereby stimulating vascularization and bone formation during jawbone reconstruction.[99] MMPs target the ECM to regulate H-type vascular growth or aging. They promote M2 macrophage infiltration and EC proliferation and differentiation, thus enhancing immune regulation and vascular generation.[100] Additionally, signaling pathways such as Hedgehog signaling,[101] HDACs,[102] Prostaglandin E2 (PGE),[103] and G Protein-Coupled Receptor Adenosine A2A[104] are involved in the EC-macrophage crosstalk that regulates H-type vessel formation. These pathways interact to amplify the effects of this crosstalk.

Furthermore, the interplay between various endogenous signals warrants further investigation. Studies suggest that the crosstalk between HIF-1α and Notch signaling enhances H-type angiogenesis and inflammatory regulation. Specifically, HIF-1α targets ligands such as Jagged1 and DLL4 to promote Notch transduction, inhibiting ECs apoptosis induced by pro-inflammatory factors and stimulating angiogenesis.[105,106] HIF-1α and HIF-2α are differentially expressed under varying hypoxic conditions, with both highly enriched in promoting the migration of ECs and macrophages, through complementary actions, they indirectly interact with the OPG/RANKL pathway, further stimulating bone marrow-derived macrophage (BMM) proliferation and differentiation.[107] In inflammatory environments, integrin α1β1 and α5β1 crosstalk with the highly activated Wnt/β-catenin pathway, upregulating MMP-9 to remodel the ECM. This promotes the expression of VEGF, bFGF, enabling ECs and M2 macrophages to collaboratively remodel the microenvironment, suggesting that crosstalk between signals can provide a favorable environment for EC and macrophage infiltration, thereby facilitating tissue regeneration.[108] Additionally, the crosstalk between pathways reflects the flexibility and complexity of intracellular signaling networks, allowing cells to better adapt to varying local conditions and external stimuli. Targeting the interaction of multiple pathways can enhance the precision and effectiveness of cellular responses. However, in certain special cases (such as different targets or species), H-type vascular ECs-macrophages crosstalk exhibits effects contrary to conventional understanding, but the specific mechanism is still unclear. Simultaneously, current research is primarily focused on cell experiments and animal models. Large-scale clinical models are still needed to validate these findings and determine how to accurately control target pathways and genes. Additionally, translating results from animal models into clinical practice remains a critical challenge. Therefore, further clarification of the roles of these signaling pathways in macrophage-EC interactions during H-type vessel differentiation is crucial for the development of novel therapeutic strategies (Figure 3A and B).

Crosstalk Between Endothelial Cells and Macrophages in Bone Diseases

Osteoporosis

OP is primarily characterized by increased bone resorption and microstructural degradation, leading to enhanced bone fragility and a higher risk of fractures.[27,74] Aging is a central factor in the pathological progression of OP, increasing sensitivity to inflammatory signals in an age-dependent manner. This results in the polarization of BMMs from tissue repair-associated M2 macrophages to pro-inflammatory M1 macrophages, exacerbating the chronic inflammatory

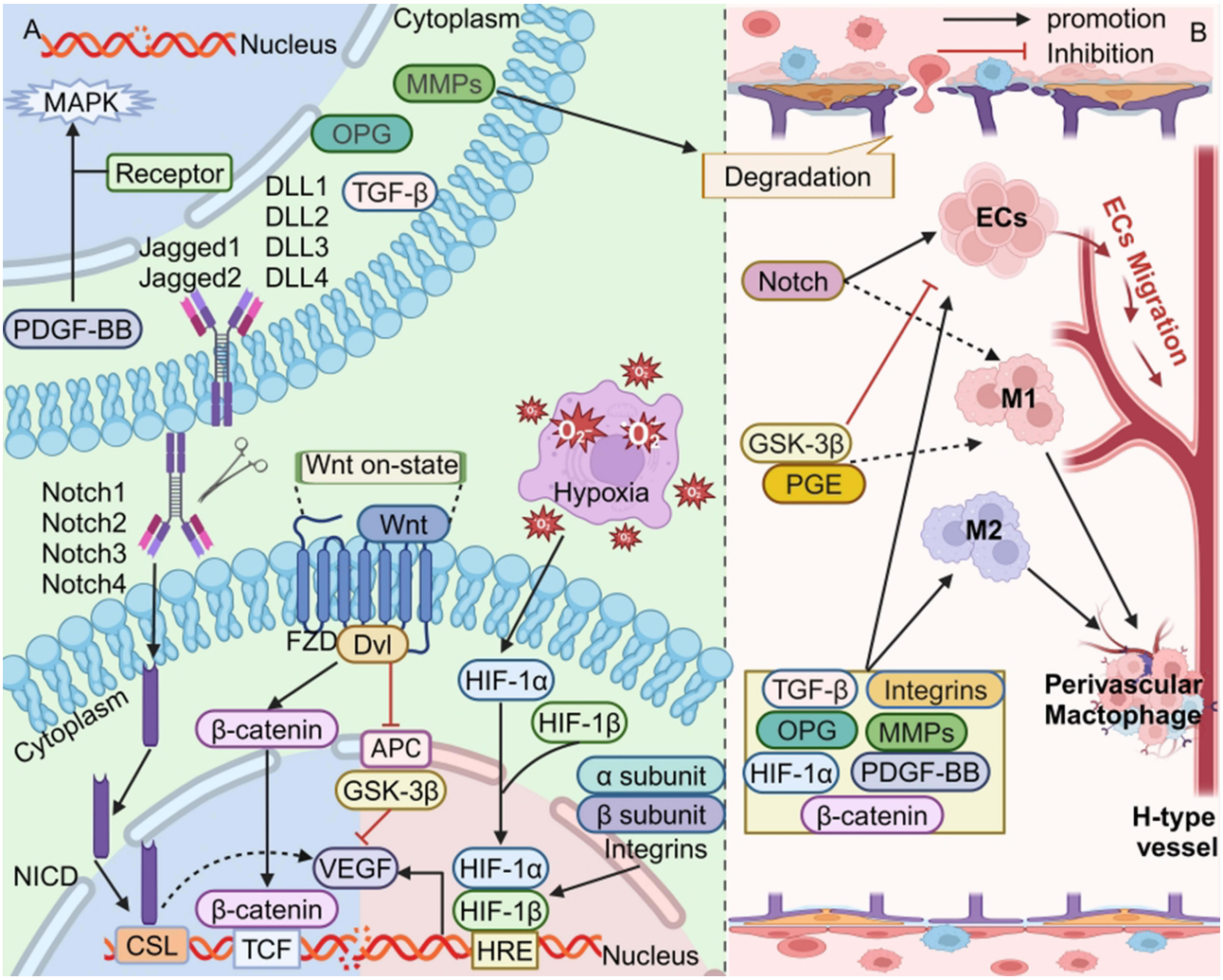


Figure 3 Mechanisms of EC-Macrophage Crosstalk in H-type Blood Vessels. (**A**) HIF-1α/VEGF, PDGF-BB, Notch, Wnt-GSK3β/β-catenin, Integrin, etc. transduction and role in endothelial cells and macrophages; (**B**) Crosstalk of Signaling Pathways in EC-Macrophage Interaction in H-type Blood Vessels. Crosstalk of Signaling Pathways drives EC migration and recruitment, as well as the differentiation of macrophages into perivascular macrophage lineages. The crosstalk between ECs and macrophages is essential for the formation of H-type blood vessels.

microenvironment. As a consequence, the number and function of ECs and OBs decline, leading to an imbalance in bone homeostasis.[109] In contrast, the infiltration of M2 macrophages promotes the release of VEGF, PDGF-BB, BMP2, and other factors, thereby accelerating bone remodeling in OP.[110] Studies have shown that Botulinum toxin type A reduces the abundance of H-type vessels and induces senile OP. Conversely, deferoxamine (DFO) intervention activates the HIF-1α pathway, stimulating H-type ECs differentiation and effectively preventing bone loss.[111] Bioactive nanoparticles can inhibit NF-κB, IL-6, and TNF-α levels in vitro, driving M2 macrophage polarization. Simultaneously, these nanoparticles stimulate VEGF expression in EPCs, promoting the recruitment of M2 macrophages and the proliferation and differentiation of ECs. This results in vascularized bone formation and facilitates OP bone repair in rabbits.[112] Additionally, treating EPCs with M2d macrophage-conditioned media inhibited responses to LPS and IL-4 stimuli, while increasing VEGFR2 and vWF levels in EPCs in a time-dependent manner. This promoted EC differentiation and maturation, ultimately improving vascular repair in OP.[113] In an OVX rat model, a strontium ion delivery scaffold upregulated VEGF, eNOS, and bFGF levels in ECs during early bone regeneration. It also suppressed IL-6, IL-1β, and TNF-α expression induced by LPS, while significantly promoting the expression of IL-10, Arg1, and PDGF-BB genes involved in vascular repair. This targeting of ECs and their crosstalk with M2 macrophages helped improve vascular repair and bone regeneration in OP.[114] In a co-culture model of macrophages and EPCs, activation of the GSK3β

signaling pathway promoted GM-CSF and NF-κB expression, driving M1 polarization and inhibiting PDGF-BB expression in ECs. This disrupted H-type angiogenesis in the inflammatory environment, accelerating bone loss.[59] Furthermore, treating BMMs from mice with pamidronate, targeting the Wnt/β-catenin pathway, inactivated M1 macrophage histone modification and DNA methylation proteins, downregulated TNF-α, IL-1α, IL-6, and other inflammatory markers, and promoted the high expression of HIF-1α, VEGFA, and BMP in ECs. This counteracted oxidative stress and ultimately improved angiogenesis-osteogenesis coupling in OP.[115] Additionally, macrophage-derived TGF-β1 coordinates EC biological behaviors by targeting and activating the HIF-1α/VEGF signaling pathway to promote H-type angiogenesis-osteogenesis differentiation and bone remodeling in OP.[116]

Fracture Healing

Fractures are caused by disruptions in bone micro-stability, morphology, and tissue perfusion. Bone healing involves multiple stages, including inflammation, repair, and remodeling, with appropriate inflammatory responses being crucial for injury recovery.[101,106] During the initiation of bone healing, macrophages and EPCs migrate, proliferate, and remodel the ECM, promoting H-type angiogenesis to optimize blood supply to the bone tissue.[117] Studies have shown that M1 macrophages are highly expressed during the early stages of vascular formation in bone healing. In the proliferative phase, M1 macrophages polarize to M2 macrophages. Simultaneously, the local hypoxic environment activates the HIF-1α/VEGF pathway, upregulating VEGFA expression, which stimulates EC proliferation and differentiation, and promotes macrophage adhesion to ECs for spatial polarization. The interaction between macrophages and ECs accelerates vascular healing and maturation.[59] Furthermore, targeted activation of HIF-1α can improve the tricarboxylic acid cycle, promote metabolic reprogramming of M2 macrophages, alleviate LPS-induced inflammatory damage and oxidative stress, significantly upregulate VEGF and CD31 levels, and enhance both angiogenesis and osteo-genesis.[118] Another study found that the infiltration of $CD163^+$ M2 macrophages is a prerequisite for re-modeling blood vessels, promoting vascularized bone formation, and repairing injured tissue.[119] Early in tibial fracture healing in mice, inhibiting TNF-α and MIP-1α overexpression upregulated VEGF, MMP-13, and BMP2 levels, suppressed M1 macrophage infiltration, and promoted EC-mediated vascular invasion and ECM degradation, enhancing angiogenesis-osteogenesis coupling to promote fracture repair.[100] In the process of femoral fracture regeneration in mice, TGF-β derived from BMMs was upregulated, stimulating the expression of intracellular kinase substrates such as Smad proteins and VEGFA in ECs, inhibiting NF-κB mediated inflammatory damage, and promoting H-type angiogenesis-osteogenesis coupling.[120] In a mouse tibial fracture model, $CD206^+$ M2a macrophages were recruited to the healing tissue, stimulating PDGF-BB pathway activation, suppressing mitochondrial ROS release, improving oxidative stress near the periosteum, and inducing H-type angiogenesis.[70] Additionally, mucin-induced activation of PDGF-BB in the femoral fracture region of mice inhibited the expression of IL-1β, IL-6, and TNF-α, reduced inflammation caused by M1 macrophage infiltration, and restored damaged H-type vessel repair and bone reconstruction. This suggests the critical role of PDGF-BB in EC-macrophage crosstalk in H-type vessels.[72]

Nontraumatic Osteonecrosis of the Femoral Head

Nontraumatic osteonecrosis of the femoral head (NONFH) is a prevalent condition among young and middle-aged individuals, characterized by insidious onset, rapid progression, and a high disability rate, thereby referred to as "Undead Cancer". NONFH is primarily associated with femoral head necrosis resulting from corticosteroid use, alcoholism, or other unknown causes.[121] Steroid-induced avascular necrosis of the femoral head (SANFH) is caused by large doses or prolonged use of glucocorticoids, leading to EC and osteocyte apoptosis. It is closely associated with blood flow dysregulation, immune imbalance, and metabolic disturbances.[4,16] SANFH is characterized by local ischemia and hypoxia, which trigger high expression of inflammatory factors such as TNF-α and NF-κB. This results in excessive M1 macrophage infiltration and the formation of a pro-inflammatory microenvironment that disrupts angiogenesis and vascularized bone formation.[122] The hypoxic environment inhibits prolyl hydroxylase-mediated degradation of HIF-1α, thereby activating the HIF-1α/VEGF pathway in ECs. This downregulates IL-4 and IL-5 while promoting VEGF and Ang1 expression, which mitigates inflammatory damage to angiogenesis.[123] Crosstalk between HIF-1α and Notch1 signaling has been shown to bidirectionally regulate macrophages under different conditions, playing a crucial role in

H-type Angiogenesis-osteogenesis coupling during femoral head repair.[124] In contrast, M2 macrophages play a critical role in femoral head re-pair by coordinating the interaction between ECs and factors such as VEGF and TGF-β, promoting ECM degradation and bone remodeling.[2] A study using a lithium-delivery bone immune biomaterial platform in a rabbit SANFH model promoted M2 macrophage polarization, upregulated VEGF and BMP2 levels, and improved bone immune responses and angiogenesis, thereby facilitating bone regeneration at the defect site.[125] Additionally, in the rabbit SANFH model, chemokine ligand 2 activates the HIF-1α/VEGF pathway, synergistically promoting crosstalk between M2 macrophages and ECs, enhancing angiogenesis and bone regeneration.[126]

Alcohol-induced osteonecrosis of the femoral head (AIONFH) is primarily caused by long-term excessive alcohol consumption, which disrupts bone circulation and leads to metabolic imbalance in osteocytes. As the second leading cause of NONFH, after glucocorticoid use, alcohol has been shown to suppress HIF-1α/VEGF signaling, downregulate the levels of VEGF and FGF2, inhibit the proliferation and migration of BMSCs and ECs, and promote mammalian target of rapamycin (mTOR)-mediated inflammatory damage, thereby driving the progression of AIONFH.[127] Chronic alcohol exposure silences Notch signaling, downregulates BMP2 secretion by ECs, and accelerates the senescence of BMSCs and ECs, leading to H-type vascular damage and the development of AIONFH. Conversely, rescuing alcohol-induced suppression of H-type angiogenesis can improve the inflammatory microenvironment, stimulate new bone formation, reduce fat accumulation, and prevent AIONFH.[128] Macrophages play a central role in regulating bone immunity by sensing tissue damage and releasing cells and chemokines. They are pivotal during the onset of AIONFH. Studies show that chronic ethanol exposure promotes a shift from oxidative phosphorylation to a glycolytic phenotype.[129] Reducing alcohol exposure affects the activation of the HIF-1α/VEGF pathway, inhibits oxidative stress, and induces M2 macrophage polarization, thereby promoting H-type vascular maturation and bone repair.[130] Moreover, inhibiting excessive alcohol consumption prevents the accumulation of ROS near the femur, enhances ECs activity, and promotes the release of factors such as IL-10, TNF-β, M-CSF, and VCAM-1, and increases H-type vessel permeability to prevent AIONFH pathogenesis.[131]

Osteoarthritis

OA is characterized by the destruction of articular chondrocytes, progressive cartilage degeneration, vascular invasion in the subchondral bone, and an imbalance in bone remodeling. Abnormal H-type angiogenesis-osteogenesis coupling leads to subchondral bone sclerosis, cyst formation, and osteophyte development, there-by driving the pathological progression of OA.[7,8,14] H-type vascular infiltration of subchondral bone is an important manifestation of early OA. Its abundance is positively correlated with subchondral bone hyperplasia and sclerosis, and H-type vessels stimulate ECM absorption to promote cartilage degeneration.[132,133] Studies have shown that activation of mTOR in chondrocytes can up-regulate VEGF levels and stimulate H-type angiogenesis, and then the coupling with bone formation leads to abnormal subchondral ossification and induces OA.[134] Simultaneously, the proliferation ability of EPCs and BMSCs and the number of H-type vessels in the "bone island" area formed by OA increased significantly, suggesting that abnormal H-type angiogenesis-osteogenic coupling promoted the pathological progress of OA.[13] In a mouse anterior cruciate ligament excision model, Halofuginone has been shown to mitigate abnormal H-type vascular formation by inhibiting the TGF-β/Smad2/3 signaling pathway. This helps preserve the normal microstructure of the subchondral bone and prevent the onset of OA.[97] Mechanical overload in the anterior cruciate ligament-injured mouse model promotes macrophage polarization via M-CSF, increasing the expression of MMP-2 in ECs. This results in abnormal H-type vascular-osteogenesis differentiation and exacerbates cartilage erosion in OA.[135] In a human knee OA model, inhibiting OPG/RANKL signaling upregulates TNF-α and IL-6, facilitating M1 polarization. This also increases VEGF and MMP-9 levels in a concentration-dependent manner, further promoting abnormal H-type vascularization and bone formation, thus worsening OA pathology.[136] Additionally, in a high-fat diet-induced OA mouse model, metformin suppresses COX-2/PGE2 signaling, reduces M1 macrophage infiltration in the subchondral bone, and diminishes EC recruitment and the number of abnormal H-type vessels. This restores bone formation and improves the pathological condition of OA.[137] These findings highlight the interplay between H-type vascular ECs and macrophages as a critical factor in the progression of OA.

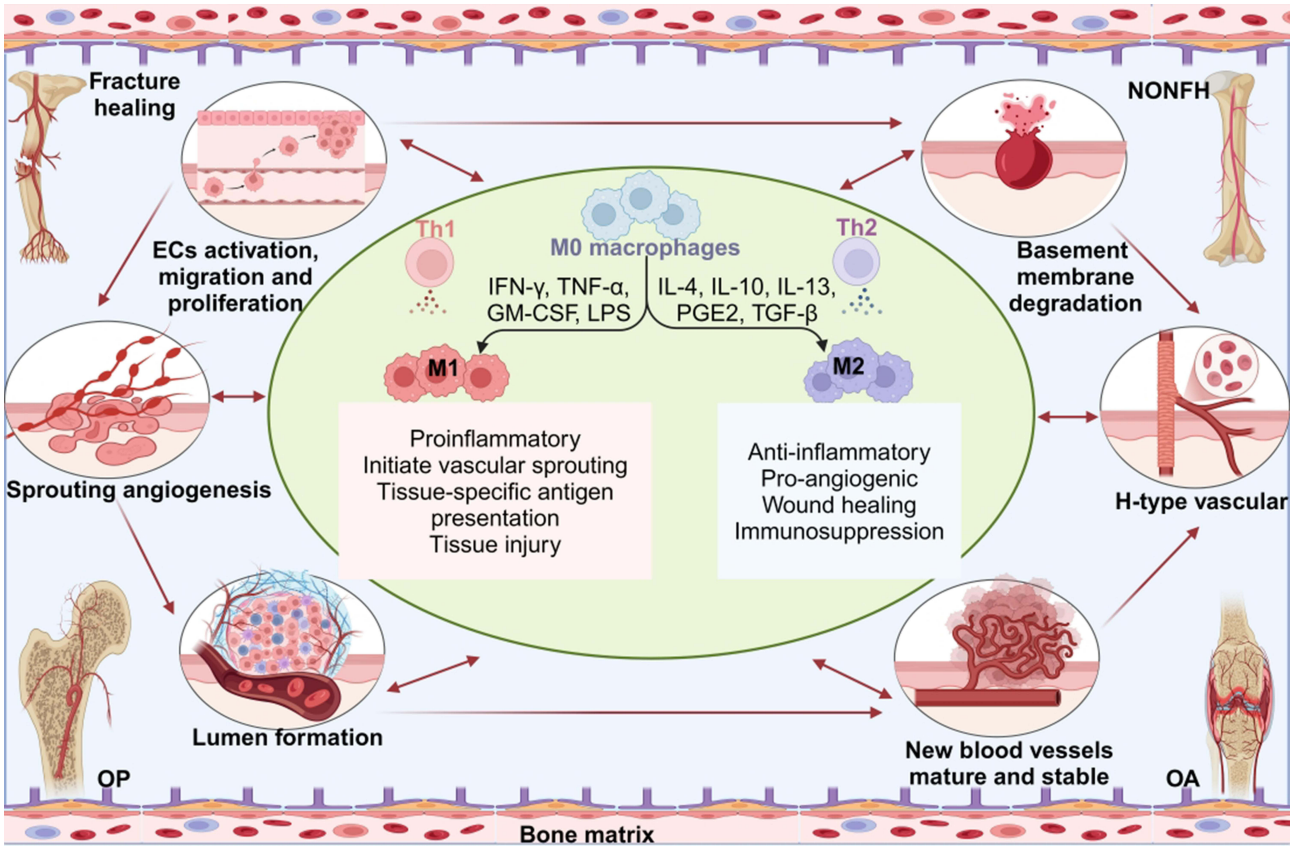


Figure 4 H-type Vascular EC-Macrophage Crosstalk in Bone Disease. During the repair of bone metabolic diseases, including OP, OA, NONFH, and fracture healing, ECs first differentiate into H-type ECs characterized by specific markers. These H-type ECs then proliferate, differentiate, and migrate to specific bone regions, where they promote angiogenesis and matrix degradation/remodeling. As new blood vessels form and the lumen develops, H-type blood vessels mature and stabilize, forming a distinct structural and functional vascular network. This process is accompanied by the polarization of macrophages into distinct phenotypes. The crosstalk between H-type ECs and macrophages plays a crucial role in maintaining bone homeostasis and facilitating the repair and remodeling of metabolic bone diseases.

In summary, H-type vascular EC-macrophage crosstalk plays an important role in various bone metabolic diseases Figure 4.

Strategies for Restoring Bone Homeostasis Imbalance

Exosomes

Exosomes (Exos) are emerging as novel "acellular therapeutics" carrying nucleic acids, lipids, and other bioactive molecules within membrane-bound vesicles. They exert therapeutic effects through receptor-ligand binding and fusion-mediated endocytosis, delivering non-coding RNAs and bioactive molecules to disease targets. By facilitating the migration and proliferation of macrophages and H-type vascular ECs, exosomes hold promise as a potential tool for maintaining bone homeostasis. Exosomes derived from macrophages and BMSCs demonstrate high targeting specificity, low immunogenicity, and safety[3,31,98] (Table 1). However, their multi-target and multi-pathway effects result in complex crosstalk, highlighting the need for further research into the mechanisms that activate H-type angiogenesis-osteogenesis coupling. Additionally, translating findings from animal models to clinical practice and improving in vivo cellular targeting and efficient uptake remain key challenges for this therapy.

Natural Active Monomers

Natural bioactive components are recognized for their multi-target properties and high safety profiles. These compounds regulate angiogenesis-osteogenesis coupling by targeting the crosstalk between H-type vascular ECs and macrophages, offering promising avenues for clinical treatment (Table 2).

https://doi.org/10.2147/JIR.S502604

Table 1 The Effect and Mechanism of Exosomes on H-Type Vascular ECs-Macrophages Crosstalk

Source of Exos	Models	Mechanism	Effect	Ref.
M2 macrophage-Exos	Bone defect rats	Activation of HIF-1α/VEGF, up-regulation of VEGF, PDGF-BB, Arg1 and IL-4	Promote angiogenesis-osteogenesis coupling and M2 polarization	[138]
M2 macrophage-Exos	SANFH rats	Inhibition of TNF-α, IL-6, up-regulation of VEGF, OCN	Inhibit M1 infiltration and promote EC migration	[139]
M2 macrophage-Exos	Dental pulp necrosis mice	Up-regulation of TGF-β, VEGF, CD163, Ang, PDGFA	Drive M2 polarization, EC migration and proliferation	[140]
BMM-Exos	Jaw necrosis mice	Stimulation of G protein Rap1, VEGFR2 pathway transduction; inhibition of NF-κβ	Inhibit M1 polarization and promote H-type angiogenesis-osteogenesis	[141]
Macrophage-Exos	Tibial fracture rats	Activation of adenosine receptor A2A transduction, up-regulation of vWF, CD31	Promote the proliferation and differentiation of ECs.	[142]
BMSCs-Exos	Femoral fracture mice	Promotion of Arg1, TGF-β, IL-10, VEGFA, CD34	Drive M2 polarization and promote EC migration and proliferation.	[143]
BMSCs-Exos	Lumbar arthritis mice	Inhibition of RANKL / RANK pathway; promotion of proteoglycan and MMP13	Reduce local inflammatory response; promote H-type angiogenesis	[144]
Human serum-Exos	Mandible defect mice	Activation of integrin α2; Down-regulation of IL-6, IL-1β, CD86, up-regulation of VCAM1	Inhibit M1 polarization; promote H-type angiogenesis	[145]

Other Avenues

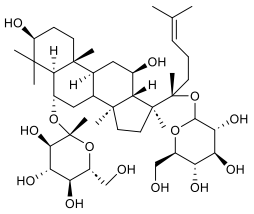
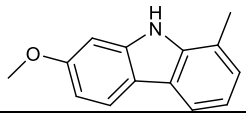
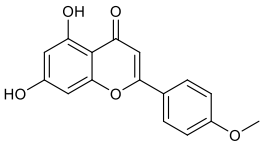
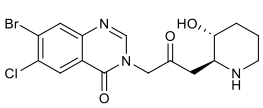
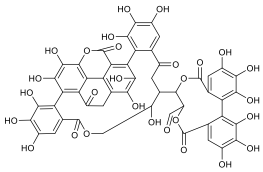
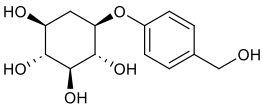
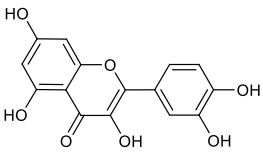
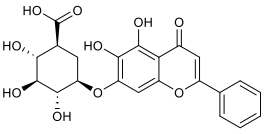
Recent advancements in biomaterials have provided effective strategies for regulating the bone microenvironment and promoting bone regeneration. For instance, nano-composite hydrogels implanted into femoral fracture models in mice activate HIF-1α signaling, upregulating VEGF, CD206, and other markers. This reprograms macrophage and EC metabolism, promoting M2 polarization and enhancing vascular and bone healing.[153] Simultaneous incorporation of strontium into titanium nanoparticles upregulates intracellular levels of HIF-1α and PDGF-BB, effectively stimulating M2 polarization and H-type vascular re-generation.[154] Similarly, calcium phosphate bioceramics used in a tibial bone loss mouse model stimulate VEGF and CD301b signaling, activating downstream IL-1 and Arg1 pathways, thereby promoting angiogenesis-osteogenesis differentiation.[155] These findings suggest that tissue engineering strategies targeting the crosstalk between H-type vascular ECs and macrophages open new avenues for angiogenesis and tissue re-generation.

DFO, a specific iron chelator and HIF-1α activator, has demonstrated efficacy in inhibiting iron accumulation, inflammation, and oxidative stress. By initiating the HIF-1α/VEGF signaling pathway, DFO recruits EPCs, stimulates EC proliferation and migration, and enhances BMP2, OPG, and downstream angiogenic factors. This promotes vascularization, tissue perfusion, and new bone formation during bone re-modeling.[156,157] In a rat bone defect model, DFO treatment activated the HIF-1α/VEGF pathway, accelerating ROS clearance and upregulating the expression of VEGF, bFGF, and TGF-β1 in a pH- and heat-dependent manner. This intervention promotes M2 macrophage reprogramming, improves the immune microenvironment, and accelerates vascular reconstruction and bone healing.[158]

Discussion and Conclusion

The crosstalk between H-type vascular ECs and macrophages is a complex and intricate process that requires a nuanced understanding. Exploring the role of macrophages in H-type angiogenesis from both micro- and macro-perspectives, including the impact of epigenetic changes, metabolic reprogramming, and environmental physical stimuli, will help

Table 2 Role of Natural Active Monomers in H-Type Vascular Endothelial Cell-Macrophage Crosstalk

Active Monomer	Chemical Structural Formula	Mechanism	Effect
Ginsenoside Rg1[114,146]		Promotion of PDGF-BB, BMP2, TGF-β1	Promote M2 polarization, proliferation of ECs
Harmine[147,148]		Promotion of PDGF-BB	Enhance spatial attachment of BMMs to ECs
Acacetin[74]		Inhibition of GSK3β, NF-κB, Promotion of PDGF-BB, OPG	Promote proliferation and differentiation of M2, ECs
Halofuginone[97]		Inhibition of TGF-β, MMP-13, A disintegrin	Inhibit macrophage polarization; proliferation of ECs
Punicalagin[149]		Promotion of VEGF, CD31; Inhibition of TNF-α	Promote proliferation and differentiation of M2, ECs
Gastrodin[150]		Promotion of VEGF, bFGF, Arg-1	Promote proliferation and differentiation of M2, ECs
Quercetin[151]		Inhibition of NF-κB	Inhibit of M1 macrophage polarization; promote of EC proliferation and differentiation
Baicalin[152]		Inhibition of MMP-9, VEGF	Promote of M2 polarization to M1; Inhibit of EC proliferation

refine the mechanisms underlying the "H-type vascular ECs-macrophage immune modulation axis" in bone diseases. Such insights could enhance our understanding of bone remodeling and open new therapeutic avenues for bone metabolic disorders.[159] Furthermore, clarifying the roles of key signaling pathways, such as HIF-1α/VEGF, PDGF-BB, Notch, and Wnt-GSK3β/β-catenin, in regulating H-type vascular ECs-macrophages interactions will deepen our understanding of how to target these pathways to improve the wound-healing environment. Targeted modulation of these pathways could facilitate the migration, recruitment, proliferation, and differentiation of macrophages and ECs, thus maintaining bone homeostasis and providing potential biomarkers for early disease diagnosis. These approaches may also lead to new

https://doi.org/10.2147/JIR.S502604

therapeutic strategies for bone diseases, including OP, SANFH, and OA. Neurotrophic factors like Netrin-1 and brain-derived neurotrophic factor regulate EC differentiation and macrophage heterogeneity, highlighting the role of peripheral nerves in bone microenvironments.[140,160,161] This could extend the traditional "angiogenesis-OB-OC" triad theory to a "peripheral nerve-angiogenesis-OB-OC" quadripartite model. Clinical studies have also demonstrated that macrophage-derived TNF-α and EC-associated TNFR2 activation significantly modulate neutrophil migration, promoting host defense and tissue homeostasis,[162] further emphasizing the importance of systemic inflammation control in bone healing. However, it is important to note that most of these findings are primarily based on animal and cell models, and large-scale clinical trials are needed for validation.

With advancements in modern fermentation and isolation techniques, natural bioactive components have emerged as alternative therapeutics targeting the crosstalk in bone metabolic diseases. However, challenges such as instability, rapid metabolism, and low bioavailability limit their clinical translation. Recent developments in nano-delivery platforms offer promising solutions to enhance the stability and bioactivity of these components, promoting H-type vascular EC-macrophage crosstalk and improving bone homeostasis. For example, Yang et al[151] used a mesoporous nanoparticle delivery system containing quercetin to treat alveolar bone defects, demonstrating its ability to inhibit NF-κB activation and suppress M1 macrophage polarization, thereby improving the bone immune microenvironment and promoting angiogenesis-osteogenesis differentiation. Similarly, Han et al[152] found that baicalin-loaded nanoparticles increased solubility, reduced oxidative stress, and targeted BMMs and ECs, enhancing the angiogenic microenvironment.

Therefore, nanodrug delivery systems can improve the solubility of active ingredients, coordinate the immune response, and achieve targeted controlled release and precise drug delivery. Nevertheless, the development of drug delivery systems that promote bone healing remains a significant challenge. A comprehensive understanding of the interactions between H-type vascular ECs and macrophages in targeted nano-delivery systems is crucial for optimizing their design and properties to enhance bone repair. However, the construction of drug delivery systems to promote bone healing remains a major challenge. Comprehensive control of nanomedicine delivery devices targeting H-type vessel ECs-macrophages crosstalk will be essential to optimize design and properties to promote bone repair. Research indicates that loading microneedle materials onto a ROS-sensitive nano-delivery system containing Astragalus membranaceus polysaccharides significantly enhances membrane penetration, promotes orderly dispersion, and inhibits ROS/NF-κB pathway activation to promote M2 macrophage infiltration and ECs proliferation, thereby supporting the orderly formation of new blood vessels.[163] The asiaticoside nanofiber delivery device dynamically and accurately controls the transformation of inflammation to the proliferation stage through $Mg2^{+}$ surface chemical modification, triggers ECs to form a complete vascular network and preferentially targets the bioactive niche to promote tissue regeneration.[164] Therefore, future efforts should consider optimizing material shape, surface modification, and drug loading capacity to maximize the restoration of bone homeostasis, paving the way for clinical translation. Meanwhile, translating these approaches into human models remains a significant challenge. (1) The preparation of nanocarriers is complex, which poses significant challenges to large-scale production for clinical use. Further research is needed to optimize production methods for clinical application; (2) exosomes loaded with monomeric components have gained widespread attention in recent years. By modifying their physicochemical properties, these exosomes can significantly enhance targeting capabilities.[165] However, exosomes derived from different sources exhibit varying membrane surface proteins, which complicates their screening and utilization. Thus, further investigation is required to optimize the extraction and modification processes of exosomes for drug loading and targeted delivery. (3) Most traditional Chinese medicine (TCM) compound ingredients exhibit significant differences in their physicochemical properties, and nanocarriers may be difficult to achieve co-loading of compound drugs. So, the development of nano-delivery systems capable of co-delivering multiple TCM components is imminent; (4) Whether the stability of the nano-delivery system can be ensured during production, transport and storage when prepared into the appropriate dosage form needs to be further investigated.

Traditional tissue engineering designs have often overlooked the role of the bone immune microenvironment, leading to suboptimal outcomes. Recent advances in biomaterials have transitioned from "immune-inert" to "immune-modulatory" designs, offering strategies such as early and transient M1 macro-phage activation to better modulate inflammatory responses and initiate H-type vascular EC-macrophage crosstalk. For example, Chen et al[166] used silica nanomaterials to treat rat cranial bone defects, employing thermal stimulation to activate M1 macrophages early, which enhanced

angiogenesis and nutrient deposition. This set the foundation for subsequent VEGF, PDGF-BB, and eNOS expression, facilitating the recruitment of ECs and M2 macrophages. Wang et al[167] applied mannan-modified titanium scaffolds in mouse bone defects, where M1 macrophage-induced mild inflammation promoted earlier angiogenesis-osteogenesis differentiation. Xu et al[168] found that biphasic biomimetic bone membranes maintain M1 macrophage recruitment to ECs during acute bone fractures, initiating angiogenesis. This process was followed by M2 macrophage polarization and the paracrine secretion of PDGF-BB and BMP2, which synergistically enhanced angiogenesis-osteogenesis coupling. These strategies effectively establish an early, favorable immune microenvironment and hold promise for coordinating immune and vascular responses to support bone regeneration. However, the physicochemical properties of certain biomaterials and the inflammatory responses during implantation must be considered. Therefore, controlling the release of M2 polarization regulators at appropriate time points will help sustain early inflammation and facilitate the timely transition to M2 macrophages, enabling precise immune modulation. However, its clinical application is still limited by several challenges. A key issue is optimizing and modulating the intensity and timing of M1 and M2 polarization to align with the natural processes of angiogenesis-osteogenesis coupling. This remains a critical focus for advancing the clinical translation of bone tissue engineering materials. Future efforts should focus on the design of biomimetic materials that incorporate bioactive molecules to maintain an appropriate early inflammatory response and promote the sequential polarization of macrophages, thereby facilitating H-type angiogenesis and bone regeneration; The preparation of advanced bone tissue materials should involve the precise design of sequential delivery strategies to facilitate phenotypic transitions during natural bone healing. This approach could provide new insights into regenerative medicine.

Moreover, stem cell therapies rooted in regenerative medicine provide novel strategies for precision treatment. Recent studies have demonstrated that dental pulp-derived mesenchymal stem cells can target and promote EC proliferation and M2 macrophage infiltration in hypoxic conditions, thereby facilitating vascular remodeling.[169] Accordingly, future research should prioritize the targeted application of highly accessible, pluripotent, and self-renewing stem cells in the interaction between H-type ECs and macrophages. Furthermore, considering the functional heterogeneity of macrophages, future studies should employ advanced methodologies such as single-cell sequencing, spatial genomics, and spatial proteomics to dynamically dissect the mechanisms of H-type vascular EC-macrophage crosstalk. By integrating single-cell RNA sequencing, spatial transcriptomics, and PhenoCycler spatial proteomics, a 3D multi-omics analysis of various macrophage types could be achieved.[170] This would provide a spatial understanding of the bone immune microenvironment, offering a novel perspective on the spatial heterogeneity of macrophages. It would also elucidate the central role of EC-macrophage communication in the bone microenvironment. Additionally, combining macromodels could further deepen our understanding of how these interactions regulate bone homeostasis, shedding light on the personalized characteristics of bone metabolic diseases and offering theoretical support for precision medicine.

In conclusion, a comprehensive understanding of H-type vascular ECs-macrophages crosstalk will guide the development of therapeutic strategies aimed at modulating tissue environment and regulating angiogenesis-osteogenesis coupling. This research holds significant promise for identifying key therapeutic targets and interventions to enhance bone homeostasis and promote bone repair in clinical settings.

Abbreviations

ECs, Endothelial cells; CD31, Platelet endothelial cell adhesion molecule-1; EMCN, Endothelial mucin; HIF-1α, Hypoxia inducible factor-1 alpha; VEGF, Vascular endothelial growth factor; PDGF-BB, Platelet-derived growth factor-BB; GSK3β, Glycogen synthase kinase 3 beta; ECM, Extracellular matrix; VCAM1, Vascular cell adhesion molecule 1; vWF, von Willebrand factor; M-CSF, Macrophage colony-stimulating factor; GM-CSF; Granulocyte-macrophage colony-stimulating factor; CSF1, Colony stimulating factor 1; ALP, Alkaline phosphatase; OCN, Osteocalcin; BMSCs, Bone marrow mesenchymal stem cells; EPCs, Endothelial progenitor cells; OB, Osteoblast; OC, Osteoclast; BMP, Bone morphogenetic protein; OPG, Osteoprotegerin; COL1A1, Type I collagen α1; Ang1, angiopoietin-1; bFGF, Basic fibroblast growth factor; DNMT, DNA methyltransferase; IL, Interleukin; TNF-α, Tumour necrosis factor alpha; HDAC, Histone deacetylase; ROS, Reactive oxygen species; NF-kB, Nuclear factor kappa-B; FA, Fatty acid; eNOS, Endothelial nitric oxide synthase; Arg1, Arginase 1; MIP, Macrophage inflammatory protein; DLL, Delta-Like; NICD, Notch intracellular domain; RBP-J, Recombination signal-binding protein-J; RANKL, Receptor activator of nuclear

factor-κ B ligand; PGE, Prostaglandin E2; mTOR, mammalian target of rapamycin; MAPK, Mitogen-activated protein kinase; BMMs, Bone marrow-derived macrophages; LPS, Lipopolysaccharides; MMP, Matrix metalloproteinases; DFO, Deferoxamine; TCM, traditional Chinese medicine; OP, Osteoporosis; NONFH, Nontraumatic osteonecrosis of the femoral head; SANFH, Steroid-induced avascular necrosis of the femoral head; AIONFH, Alcohol-induced osteonecrosis of the femoral head; OA, Osteoarthritis.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The work was supported by National Natural Science Foundation of China (No: 81860859, 82160915); Lanzhou Municipal Bureau of Science and Technology (No 2022-3-23).

Disclosure

The authors report no conflicts of interest in this work.

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