HIF-1α: Its notable role in the maintenance of oxygen, bone and iron homeostasis (Review)

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Abstract. Hypoxia is a characteristic feature of numerous diseases, including metabolic bone disease, solid tumors, cardiovascular diseases, neurodegeneration and inflammation. It is also a risk factor for a poor prognosis in various diseases. Hypoxia-inducible factor-1α (HIF-1α) is activated by hypoxia to regulate a series of pathophysiological pathways, which is of utmost significance for maintaining body homeostasis. The present review highlights the role of the HIF-1α in oxygen, bone and iron homeostasis, and alludes on the biological complexity and dual functions of HIF-1α regulation. In addition, the pathophysiological significance of HIF-1α in bone formation, bone absorption, angiogenesis, erythropoiesis, oxidative stress, energy metabolism, iron death, etc., is discussed An accurate understanding of all these processes may aid in the identification of possible therapeutic targets that may then be used in the treatment of related diseases. However, further studies are required to unravel the extensive complexity of HIF-1α regulation and to develop more precise treatment strategies.

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Abbreviations: Tf, transferrin; TFR, transferrin receptor; HO-1, heme oxygenase 1; VEGF, vascular endothelial growth factor; EPO, erythropoietin; PDK1, pyruvate dehydrogenase kinase 1; TCA, tricarboxylic acid; PHD, prolyl hydroxylase; BMSCs, bone mesenchymal stem cells; SDF-1, stromal cell-derived factor-1; CXCR4, c-X-c chemokine receptor type 4; MSCs, mesenchymal stem cells; GSH, glutathione; FGF23, fibroblast growth factor 23; GSNO, S-nitrosoglutathione

Key words: hypoxia, hypoxia-inducible factor-1α, oxygen homeostasis, bone homeostasis, iron homeostasis

Contents

1. Introduction

Hypoxia-inducible factor (HIF) heterodimers consist of one of three α-subunits (HIF-1α, HIF-2α and HIF-3α) and one β-subunit. HIF-1α, a 120 kDa polypeptide subunit that heterodimerizes with HIF-1β (a 91 to 94 kDa polypeptide subunit), is a transcription factor regulated by hypoxia (1). Under normoxic conditions, HIF-1α is hydroxylated to interact with von Hippel-Lindau (VHL) protein for ubiquitination and proteasomal degradation. HIF-1a is expressed in almost all cell types, whereas HIF-2a has a more limited distribution. Under hypoxic conditions, HIF-1α plays a crucial role in the body's metabolic and functional adaptation to these conditions. All these observations have allowed the identification of HIF-1a as a critical factor in the regulation of homeostasis. It is worth noting that in the field of integrative physiology, research on baroreflex, chemoreflex, glucose regulation and temperature regulation is essentially the study of a series of homeostasis (2-4). Among these, oxygen, bone and iron homeostasis are involved in various critical functions of the body, including bone resorption and formation, mesenchymal stem cell (MSC) homing, angiogenesis, erythropoiesis, oxidative stress, iron metabolism and ferroptosis.

Bone homeostasis is maintained by a balance between osteoblast-mediated bone formation and osteoclast-driven bone resorption (5). Under hypoxic conditions, HIF-1α exerts a series of direct and indirect effects on this balance (6). Further studies have indicated its critical role in the manipulation of bone mass accrual, bone material properties as well as micro-structures, including bone mineralization, bone collagen fiber formation and bone remodeling (7). Moreover, HIF-1α is a master regulator of oxygen homeostasis in the body, which

can induce the expression of angiogenic factors, promote glycolysis, increase the delivery of oxygen and nutrients (8). HIF-1α also plays a key role in iron homeostasis by activating the transcription of iron metabolism genes, such as transferrin (Tf), transferrin receptor (TFR), ceruloplasmin and heme oxygenase 1 (HO-1) (9,10). Roxadustat, a HIF-prolyl hydroxylase inhibitor, has been shown to improve iron metabolism in phase 3 trials (11,12).

However, over the years, although the association between HIF-1α and oxygen, bone and iron homeostasis has been the subject of increasing attention, no consensus has yet been reached on the role of HIF-1α, at least to the best of our knowledge. Research into its effects on osteocyte apoptosis and osteocyte-mediated osteoclasts has also yielded non-univocal results (13-15). In addition, the local activation of HIF-1α is required for chondrocyte survival in the center of the expanding growth plate; however, the cellular-intrinsic mechanisms remain unclear (16) The expression of the majority of HIF-1α-dependent genes contributes to the adaption of hypoxic environments in the human body. For example, the increase in the delivery of oxygen to hypoxic tissues is associated with the expression of erythropoietin (EPO) and glycolytic enzymes, which allows for the increased conversion of glucose to produce energy (17). However, HIF-1α can also play a negative role in the hypoxic process.

Overall, considering the numerous processes in which HIF-1α is involved and the yet not fully defined underlying mechanisms, the present review focused on the intimate association between HIF-1α and bone homeostasis, oxygen homeostasis, as well as iron homeostasis. In addition, the pathophysiological significance of HIF-1α in bone formation, bone absorption, angiogenesis, erythropoiesis, oxidative stress, energy metabolism, iron death, etc. is also discussed (Fig. 1). HIF-1α is a promising target for the treatment of related diseases, and further information is required to determine the clinical utility of this factor.

2. Oxygen homeostasis

HIF-1α, mediating the expression of a series of genes, has been strongly established as a critical factor for maintaining oxygen homeostasis. The regulation of oxygen homeostasis is considered to be achieved by oxygen delivery and oxygen. Oxygen delivery is involved in the control of erythropoiesis, angiogenesis and vascular remodeling. Oxygen utilization is implicated in the regulation of glucose metabolism and redox homeostasis (18).

Oxygen delivery. Vascular endothelial growth factor (VEGF) is the most potent proangiogenic factor. EPO, a glycoprotein, is considered as the principal stimulator for erythropoiesis primarily. The expression of HIF-1α is induced by a hypoxic environment, and it subsequently upregulates downstream key factors, such as EPO and VEGF, which promote angiogenesis to adapt to the environment and recover the oxygen content.

The primary cause of the ectopic overexpression of VEGF in tumors is the dysregulated expression of HIF-1α involving the c-X-c chemokine receptor type 4 (CXCR4)/stromal-derived cell factor-1 (SDF-1) axis (19). The study by Li *et al* (20) conducted on cerebral ischemic rats, found that HIF-1α attenuated neuronal apoptosis, partially by upregulating EPO expression. There is a novel molecular mechanism for the anti-angiogenic effects of peroxisome proliferator-activated receptor α, which are achieved by inhibiting ischemia-induced EPC mobilization and homing through the inhibition of the HIF-1α/SDF-1 pathway (21). Rankin *et al* (22) found that osterix-VHL mice with a deficiency in VHL in osteoblasts exhibited overexpressed HIFs, accompanied by a significant increase in circulating red blood cells. Gerri *et al* (23) reported that HIF-1α regulated hematopoietic stem cells upstream of the Notch signaling pathway.

Oxygen utilization. HIF-1α, in response to hypoxic irritation, participates in the regulation of glucose transporters and glycolytic enzymes, which are key genes in energy metabolism and exert critical effects on cell survival (24). Moreover, HIF-1α inhibits pyruvate dehydrogenase by activating pyruvate dehydrogenase kinase 1 (PDK1), and thereby, pyruvate is redirected from the tricarboxylic acid (TCA) cycle and converted into lactate (25).

The overexpression of constitutive cardiac-specific HIF-1α leads to changes in cellular metabolism and increased glucose utilization, subsequently resulting in cardiomyopathy in aging mice (26). On the other hand, the deletion of HIF-1α in cardiomyocytes results in decreased ATP, lactate and phosphocreatine levels, and inn an impaired myocardial contractility (27). Chondrocytes maintain an optimal energy balance during endochondral ossification, which is achieved by confined HIF-1α signaling (28). However, it is only under hypoxic conditions that glucose uptake and bone resorption can be affected by HIF-1α knockdown. HIF-1α promotes glycolysis during hypoxia; however, it also affects metabolism under normoxic conditions. A decreased HIF-1α activity also has effects on mitochondrial metabolism that results in mitochondrial loss and lipid accumulation, along with reduced oxidative phosphorylation and fatty acid metabolism (26,29). In addition, studies have demonstrated that HIF-dependent metabolic processes can also modulated by dimethyloxalylglycine, desferrioxamine, prolyl hydroxylase (PHD) and other small molecules (30,31).

Oxidative stress. HIF-1α is an endogenous anti-oxidative stress modulator. The oxidative stress pathway induces the activation of HIF-1α, and increases the production of mitochondrial complex II-mediated reactive oxygen species (ROS) (32,33). Moreover, it has been demonstrated that increased superoxide anion radicals induce PHD inactivation, resulting in the stabilization and accumulation of HIF-1α (34). Under hypoxic conditions, HIF-1α dynamically regulates glucose flux through the glycolytic pathway to resist the increased risk of ROS production and confers protection against apoptosis and renal injury in diabetes (35,36).

In recent years, increasing evidence has indicated that HIF-1α can enhance antioxidant activity and neuroprotection (37,38). HIF-1α has the ability to mitigate this toxicity or regulate redox homeostasis by limiting TCA activity, regulating the levels of NADPH and glutathione (GSH), and reducing mitochondrial mass through the upregulation of the

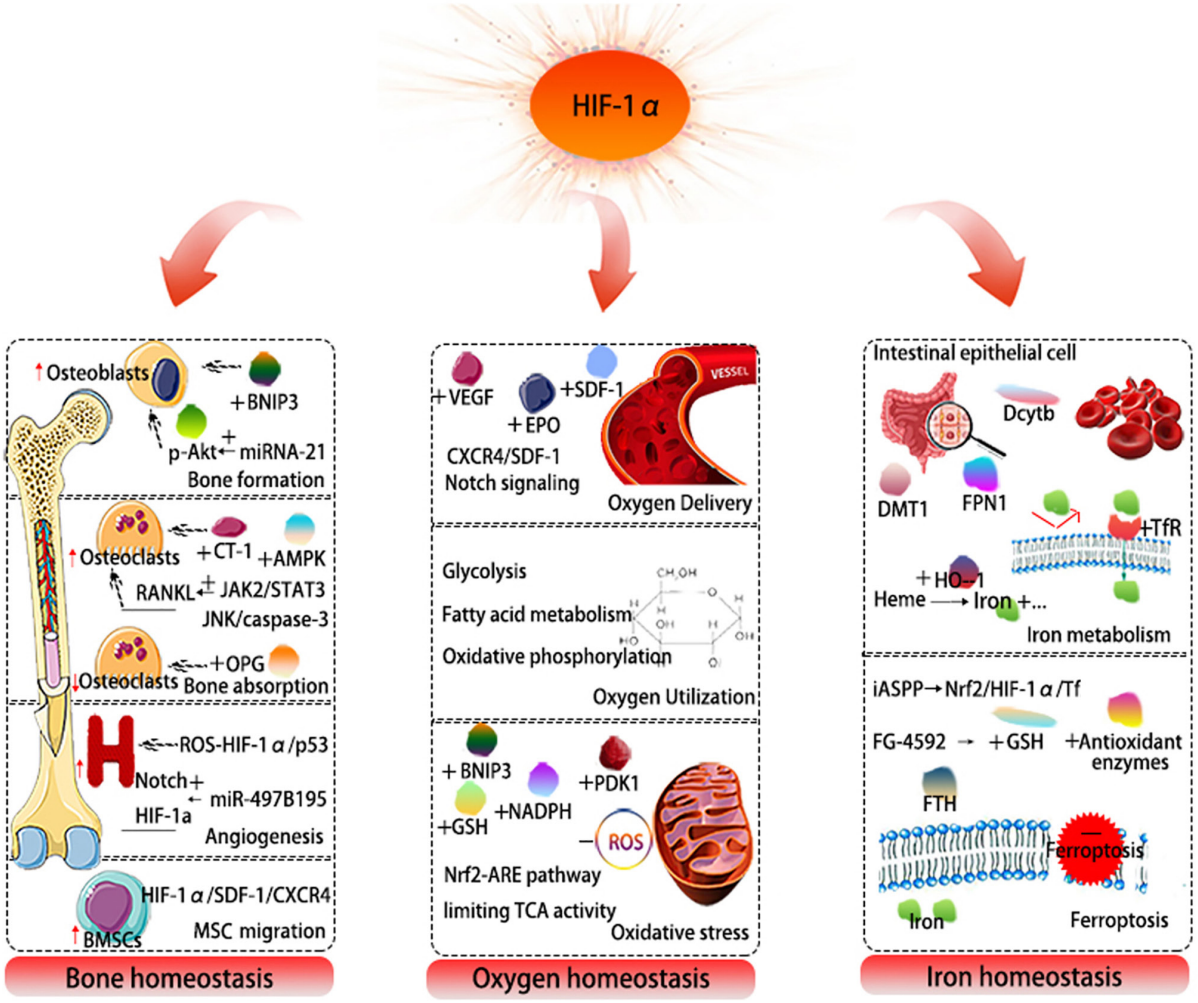

Figure 1. Role of the HIF-1α in oxygen homeostasis, bone homeostasis, and iron homeostasis. +, indicates increased expression; ↑, promoting function; ↓, inhibitory function; HIF-1α, hypoxia-inducible factor 1 α; BNIP3, Bcl-2 interacting protein 3; CT-1, cardiotrophin-1; RANKL, receptor activator of nuclear factor κB ligand; OPG, osteoprotegerin; ROS, reactive oxygen species; SDF-1, stromal cell-derived factor-1; CXCR4, c-X-c chemokine receptor type 4; MSC, mesenchymal stem cell; BMSCs, bone mesenchymal stem cells; VEGF, vascular endothelial growth factor; EPO, erythropoietin; PDK1, pyruvate dehydrogenase kinase 1; GSH, glutathione; TCA, tricarboxylic acid; Dcytb, duodenal cytochrome B; DMT1, divalent metal transporter 1; FPN1, ferroportin1; iASPP, inhibitor of apoptosis-stimulating protein of p53; Nrf2, nuclear factor erythroid 2-related factor 2; Tf, transferrin.

mitochondrial proteins, PDK1 and Bcl-2 interacting protein 3 (BNIP3) (39). Furthermore, HIF-1α may be an indirect player in the promotion of mitochondrial-selective autophagy and may subsequently lower the mitochondrial mass, which inhibits the oxidation of both glucose and fatty acids, and reduces mitochondrial ROS production under hypoxic conditions (40). A previous study revealed that HIF-1α can activate the nuclear factor erythroid 2-related factor 2 (Nrf2)/ARE pathway to protect against ischemia-reperfusion cardiac and skeletal muscle injuries (41).

3. Bone homeostasis

Bone formation. Previous research has indicated that HIF-1α may affect the osteogenesis of osteoblasts through the prevention of chondrocyte cell death in the growth plate, and also via direct or indirect actions on the delivery of oxygen and nutrients, together with metabolic adaptations (8). It has been reported that the overexpression of HIF-1α, through its downstream marker, BNIP3, reduces the inhibitory effects of dexamethasone on hypoxia-induced mitophagy and protects osteocytes from apoptosis (42). There is also evidence to suggest that miRNA-21, by upregulating the activation of HIF-1α and p-Akt, can promote the osteogenic ability of bone MSCs (BMSCs) (43). HIF-1α does not only promote osteogenesis, but also has repairing effects on bone (44). Moreover, it has been demonstrated that prolonged HIF-1α signaling in chondrocytes, interfering with cellular bioenergetics and biosynthesis, results in skeletal dysplasia by collagen overmodification (27).

Bone resorption. The delicate balance between osteoblastic bone formation and osteoclastic bone resorption is a key factor in the regulation of mature bone tissue formation (45). Nevertheless, no consensus has yet been reached on the role of HIF-1α in regulating osteoclast differentiation, at least to the best of our knowledge.

Promotion of osteoclast differentiation. HIF-1α expression has been proposed to increase bone erosion in rheumatoid arthritis (46). HIF-1α is involved in the increase

of osteoclastogenesis and bone resorption, since it has recently been shown to enhance the osteoclast-mediated stimulation of BMSC differentiation by secreting cardiotrophin-1 (47). Moreover, HIF-1α functions by activating the JAK2/STAT3 pathway, promoting the expression of RANKL, and thus enhancing the differentiation of osteocyte-mediated osteoclastic *in vitro* (48). HIF-1α also plays a pro-apoptotic role in JNK/caspase-3 signaling pathway activation. Osteocyte-mediated osteoclastogenesis has been shown to be reduced with a concomitant decrease in HIF-1α and caspase-3 expression (49). A previous study demonstrated that the deceleration of osteoclastogenesis occurred under conditions of HIF-1α deficiency, by inhibiting AMPK signaling under anoxic conditions (50). Of note, HIF-1α knockdown reduces bone resorption under both normoxic and hypoxic conditions. Thus, the targeting of HIF-1α may prove to be of value in th treatment of osteoporosis (13).

Inhibition of osteoclast differentiation. Both the VHL/HIF and PHD/HIF signaling pathways in osteoblasts have been shown to reduce osteoclastogenesis by increasing osteoprotegerin expression and inhibiting sclerostin expression, resulting in increased bone formation and decreased resorption (14,51). In addition, it has been suggested that the activation of osteoblast HIF-1α contributes to the inhibition of osteoclastogenesis, by increasing IL-33 expression (52).

Angiogenesis. A vital role in bone remodeling and vascularization is attributed to the HIF-1α/VEGF signaling pathway (53). The study by Kusumbe *et al* (54) demonstrated endothelial HIF-1α as a critical promoter of type H vessel formation in the metaphysis. HIF-1α has also been implicated in the increased number of type-H vessels and the restoration of bone mass (55-57). The miR-497B195 cluster has been proposed to regulate angiogenesis during coupling with osteogenesis, by maintaining endothelial Notch and HIF-1α activity (58). Furthermore, HIF-1α may have a dual function in the regulation of osteogenesis-angiogenesis coupling of long bone via the ROS-HIF1α/p53 axis (59).

MSC migration. HIF-1α has also been demonstrated to trigger wound healing and functional recovery by regulating corresponding stem cells (60,61). BMSCs, a class of heterogeneous cells, have a series of feasible and diverse clinical values for generating stroma which can support hematopoiesis, bones, adipocytes and cartilage (62).

HIF-1α regulates the expression levels of surface molecules, such as SDF-1, a downstream gene of HIF-1α, which binds to its specific receptor, CXCR4, forming a pair of coupling molecules and promoting stem cell migration to ischemic and hypoxic sites (63). Guo *et al* (62) demonstrated that the HIF-1α/SDF-1/CXCR4 axis enhanced BMSC migration, and alleviated neuronal damage and apoptosis. Moreover, there is evidence to suggest that the increased secretion of HIF-1α induced by the hypoxic conditions of surrounding brain tissue accelerates the fracture repair process via chemotaxis due to the SDF-1/CXCR4 axis. In addition, the silencing of HIF-1α has been shown to decrease MSC migration, as well as the mRNA and protein levels of SDF-1 and CXCR4 in MSCs (64).

4. Iron homeostasis

Iron metabolism. HIF-1α is a vital factor in iron metabolism by regulating the expression of iron-related proteins, such as divalent metal transporter 1, ferroportin 1, duodenal cytochrome B and TFR (65,66). An overload of iron has been found to be related to the dysfunction of MSCs and to the damage of the microenvironment that may be involved in the pathogenesis of myelodysplastic syndromes, and which may be achieved by the regulation of cytokine of MSCs through the ROS/HIF-1α pathway (67). It has been demonstrated that HIF-1α induces TFR1 expression, thereby increasing iron uptake (68). In addition, it has been suggested that HO-1, induced by HIF-1α, degrades heme into biliverdin, carbon monoxide and iron (69). Weinreb *et al* (70) and Guo *et al* (71) demonstrated that in various brain regions of adult mice, the upregulation of HIF-1α by the iron chelator, M30, results in differentially induced levels of TFR, tyrosine hydroxylase and EPO (72).

Ferroptosis. Ferroptosis is a new form of regulated cell death as a result of iron-dependent lipid peroxidation (73). Moreover, HIF-1α downregulation also promotes ferroptosis by inducing ferritin heavy chain degradation in RANKL-stimulated bone marrow-derived macrophages. A previous *in vitro* study demonstrated that the overexpression of inhibitor of apoptosis-stimulating protein of p53 inhibited ferroptosis through the Nrf2/HIF-1α/TF signaling pathway (74). In another study, following pre-treatment with roxadustat (an inhibitor of HIF prolyl hydroxylase), the risk of ferroptosis was correspondingly reduced, along with increased levels of antioxidant enzymes and GSH, and decreased iron accumulation (75).

5. Summary and future perspectives

Constant oxygen supply is essential for proper tissue function, development and homeostasis. Hypoxia is a distinctive feature of diseases, including solid tumors, metabolic bone disease, cardiovascular diseases, neurodegeneration, inflammation and other chronic diseases (76,77). It is also a risk factor for a poor prognosis in various diseases. For example, hypoxia is responsible for the failure of the majority of solid tumors to respond to treatment, and promotes drug resistance (78). Under normoxic conditions, HIF is rapidly degraded by the high activity of PHDs. However, under hypoxic conditions, the shortage of oxygen results in the dimerization of non-hydroxylated and non-degradable HIF-1α with HIF-1β, which binds to hypoxia-responsive elements in the regulatory regions of oxygen-sensitive genes. Given the ubiquitous localization of HIF-1α, HIF-1α acts as a main regulator in the expression of several thousand genes coding, including growth factors, enzymes, transcription factors, cytokines, hormones, receptors, solute transporters, ion channels and other essential regulators, which are involved in almost every cell function or dysfunction (79).

There is no doubt that bone, oxygen and iron homeostasis are of utmost significance to the human body, and the role of HIF-1α in the maintenance of homeostasis cannot be ignored. Although HIF-1α plays a beneficial role in the regulation of bone homeostasis, the degree of HIF-1α pathway activation must be fine-tuned to avoid the disruption of

Table I. Mechanisms and effects of HIF-1α on various diseases.

Differential expression at protein/gene levels	Mechanisms	Effects	(Refs.)
VEGF	Chemokine receptor 4/stromal-derived cell factor 1 (CXCR4/SDF-1) axis	Promotes tumor angiogenesis	(19)
EPO	Upregulating EPO	Attenuates neuronal apoptosis	(20)
SDF-1	HIF-1a/SDF-1 pathway	Anti-angiogenic effect	(21)
PDK1	Inactivates pyruvate dehydrogenase (PDH)	Increases ATP levels and prevents toxic ROS production	(39)
NADPH and GSH	Switches cells from oxidative to glycolytic metabolism, to reduce mitochondrial superoxide generation	Maintains redox homeostasis	(40)
Nrf2	Nrf2/ARE pathway	Protects against ischemia-reperfusion cardiac and skeletal muscle injuries	(41)
BNIP3	Reduces the inhibitory effects of DEX on hypoxia-induced mitophagy	Protects bone cells from apoptosis	(42)
CT-1	Enhances the osteoclast-mediated stimulation of BMSC differentiation	Bone resorption	(47)
RANKL	JAK2/STAT3 pathway	Enhances the differentiation of osteocyte-mediated osteoclastic	(48)
IL-33	Acts on bone marrow-derived monocytes	Contributes to osteoclastogenesis inhibition	(52)
SDF-1	HIF-1α/SDF-1/CXCR4 axis	Alleviates neuronal damage and apoptosis	(62)

VEGF, vascular endothelial growth factor; EPO, erythropoietin; PDK1, pyruvate dehydrogenase kinase 1; DEX, dexamethasone; CT-1, cardiotrophin-1; IL-33, interleukin-33; SDF-1, stromal cell-derived factor-1; CXCR4, c-X-c chemokine receptor type 4; RANKL, receptor activator of nuclear factor kappa-B ligand; GSH, glutathione; BNIP3, Bcl-2 interacting protein 3; Nrf2, nuclear factor erythroid 2-related factor 2; RANKL, receptor activator of nuclear factor κB ligand.

homeostasis (8,80). Previous studies have confirmed that osteoblastic HIF-1α affects bone formation (81-83); however, its role in osteoclasts remains controversial. An interesting aspect is that HIF-1α has minimal effects on osteoclast differentiation, although it predominantly functions as a regulator of osteoclast-mediated bone resorption (84). Similarly, the knockdown of HIF-1α does not affect the process of osteoclast differentiation, although it prevents the increased bone resorption under hypoxic conditions (6). Moreover, HIF-1α has been demonstrated to regulate osteogenesis-angiogenesis coupling bidirectionally, and the effect is age-related (56). There is also evidence to suggest that HIF-1α functions by increasing EPO levels directly or indirectly, inducing the expression and processing of fibroblast growth factor23 (FGF23), and thus affecting mineral homeostasis and vitamin D metabolism (8). Of note, increased serum FGF23 levels have been reported to be associated with the reduction of serum phosphate or 1,25(OH)2D, which in turn may alter bone homeostasis, although further confirmation is required (85,86).

Taken together, HIF-1α expression is mainly induced by hypoxic stress and is common during the development of various diseases. The present review mainly focused on the role of HIF-1α in regulating oxygen, bone and iron homeostasis. Although significant progress has been made in the understanding of the pathogenesis of diseases, such as atherosclerosis and emerging drug treatments, the current treatment options continue to have a number of deficiencies. Regulating the expression and signaling pathways of HIF-1α may be a promising strategy for the treatment of diseases involving the pathophysiology of hypoxia (Table I). To date, a number of active ingredients of traditional Chinese medicine and natural products have been found to regulate the HIF-1α content (87). At present, HIF-1α inhibitors have been used to treat various diseases, such as tumors, leukemia, diabetes, ischemic cardiovascular and brain diseases, etc. Manassantin A and Manassantin B exert potent inhibitory effects on the secretion of hypoxia-induced VEGF, cyclin-dependent kinase inhibitor 1 and GLUT-1 genes (88,89). Lificiguat (YC-1) is a targeted HIF-1α inhibitor, which can reduce HIF-1α protein expression and is associated with the enhancement of EGFR degradation, thereby exerting antitumor effects (90). The benefit of S-nitrosoglutathione on traumatic brain injury is mediated by S-nitrosylation to stabilize HIF-1α (91).

Notably, immense efforts and resources have been invested in identifying possible effective and specific small-molecules inhibitors of HIF-1α. HIF-1α, as a common pathophysiological mechanism of numerous diseases, plays an exploratory role in the treatment of comorbidities. However, there are several questions and challenges involved in translating the findings from mechanobiological studies into novel HIF-1α-targeted therapeutics. The potential interaction network of multiple molecules regulates the expression of important genes.

Important interactions between NF-κB and HIF-1α (92-94) have been described recently. In addition, efficacy needs to be supported by high-quality clinical trial evidence.

HIF-1α is a master regulator of homeostasis, and plays critical roles in physiological and pathological processes. Understanding the roles and regulation mechanisms of HIF-1α in bone, oxygen and iron homeostasis may open a new era in the development of therapeutic strategies against a variety of pathologic conditions, such as metabolic bone disease, ischemic/hypoxic injuries, tumor growth, wound healing and cardiovascular remodeling.

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Availability of data and materials

Not applicable.

Authors' contributions

XW and LZ were responsible for the conceptualization of the study. XH was responsible for the research design. XH and YZ were responsible for the determination of the research design. XH and YZ wrote the manuscript. BQ, KS and NL were responsible for the literature search. BT and SF completed the references and were involved in document management and preparation. YZ and XH prepared the original draft. XW and LZ reviewed and edited the manuscript. All authors contributed to the article and have read and approved the submitted version. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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