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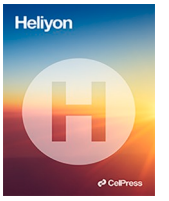

Review article

Roles of the HIF-1α pathway in the development and progression of keloids

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ABSTRACT

Keloids, a pathological scar that is induced by the consequence of aberrant wound healing, is still a major global health concern for its unsatisfactory treatment outcomes. HIF-1α, a main regulator of hypoxia, mainly acts through some proteins or signaling pathways and plays important roles in a variety of biological processes. Accumulating evidence has shown that HIF-1α played a crucial role in the process of keloid formation. In this review, we attempted to summarize the current knowledge on the association between HIF-1α expression and the development and progression of keloids. Through a comprehensive analysis, the molecular mechanisms underlying HIF-1α in keloids were shown to be correlated to the proliferation of fibroblasts, angiogenesis, and collagen deposits. The affected proteins and the signaling pathways were multiple. For instance, HIF-1α was reported to promote keloids formation by enhancing angiogenesis, fibroblast proliferation, and collagen deposition through the activation of periostin PI3K/Akt, TGF-β/Smad and TLR4/MyD88/NF-κB pathway. However, the specific effects of HIF-1α on keloids keloid illnesses in clinical practice is are entirely unclear, and further studies in clinical trials are still warranted. Therefore, an in-depth understanding of the biological mechanisms of HIF-1α in keloid formation is significant to develop promising therapeutic targets for the treatment of keloids in clinical practice.

1. Introduction

Keloids are caused by abnormal healing processes in the skin, and they are characterized by excessive growth of scar tissue [1]. The prevalence of keloids ranges from 0.09% to 16% according to different countries or regions [2]. The estimated number of sufferers with keloids are predicted with 11 million [3]. Keloids are reported by statistics to be 7–10 times more likely to cause Blacks to seek medical attention than Whites [4]. This illness may cause the physical symptoms of pain, itch, and immobility. Besides, keloids are also associated with psychological symptoms, i.e., appearance anxiety and depression. As a result, it has a negative impact on one's quality of life and everyday activities [5]. At present, there are several treatments available, including corticosteroid injections, surgery, and pressure therapy. But these managements are complex, expensive, and time-consuming [6]. What's worse, these treatments may only

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be partially successful. Therefore, a better understanding of the pathological process of keloids may help to explore effective target treatments. It was reported that fibroblasts, blood vessels, and collagen deposits played an important role in the process of keloid formation [7,8]. Fibroblasts are responsible for producing collagen, which forms the structure of the scar tissue [9]. Excessive growth of fibroblasts can lead to overproduction of collagen, which results in the raised appearance of keloids [10]. Additionally, an increase in blood vessels in the area of the keloids may also contribute to the growth of keloids [11]. Treatments for keloids typically aim to reduce the appearance of the scar tissue and may include surgical removal, steroid injections, or laser therapy [12,13]. However, the treatment effect is often suboptimal. Further research is needed to fully understand the mechanisms of keloid formation and to develop more effective treatment options.

A study in blood vessels of keloids showed that the vessels of the central region are compressed, providing only sparse, inadequate perfusion [14]. In addition, keloids showed an increase in adenosine triphosphate (ATP) levels after about ten years as a result of anaerobic glycolysis caused by the decrease in oxygen perfusion from crushed blood vessels [15,16]. Also, animal models confirmed that oxygen content in local tissue was significantly decreased during keloids formation extracellular matrix remodeling and equine dermal fibroblast proliferation [17]. It was reported that hypoxia inducible hypoxia-induced factor-1 alpha (HIF-1α) expression was highly linked with the concentration of oxygen [18]. Some previous studies have unveiled that HIF-1α, a main regulator of hypoxia, influenced not only lipid metabolism but also angiogenesis and wound healing [19–21]. Currently, HIF-1α has also been demonstrated to have an essential important role in the process of keloids [22–24]. However, the specific mechanisms of keloid formation are not yet fully understood. In this present study, we summarize the recent advances of HIF-1α in keloids.

2. Overview of HIF-1α

In 1991, Semenza et al. [25] discovered the presence of HIF protein for the first time during their research on the erythropoietin (EPO) gene. This protein constitutes a large family of transcriptional regulators and has the ability to activate the transcription of several genes related to hypoxia [25]. The HIF family has three members, namely HIF-1, HIF-2, and HIF-3 and comprises α and β subunits (HIF-1α, HIF-2α, and HIF-3α and HIF-1β) [26,27]. Among them, HIF-1α and HIF-2α are the most extensively characterized and dimerize with HIF-1β respectively, an aryl-hydrocarbon-nuclear receptor translocator (ARNT) [28]. HIF-1 is a transcriptionally active heterodimer composed of the HIF-1α and HIF-1β subunits [29]. HIF-1α is localized to cytoplasm and functions as a key transcription factor that regulates the cellular adaptive responses to hypoxia [30]. On the other hand, HIF-1β is located in the nucleus and is constitutively expressed [31]. Activation of HIF leads to the upregulation of the expression of multiple target genes to promote cellular adaptation and resistance to hypoxic environments. For example, HIF-1α is the master transcriptional factor in regulating the expression of more than 40 target genes in response to hypoxia.

The degradation or synthesis of HIF-1α is tightly regulated by different oxygen levels. In normoxic conditions, prolyl hydroxylase (PHD) enzymes can bind to HIF-1α and hydroxylate specific proline residues, contributing to the degradation by von Hippel Lindau protein (pVHL) and the proteasome [32]. Factor-inhibiting HIF-1 (FIH-1), a negative regulator of hypoxia inducible factor (HIF), has been reported to hydroxylate asparagine residue and disrupt the binding of the co-activators p300/CREB-binding protein to FIH-1, which inhibits its transcriptional activation potential [33,34]. In addition, FIH-1 can suppress transactivation by recruiting histone deacetylases through interacting with pVHL [35]. For example, Zhu et al. [36] found that the depletion of miR-31 inhibited the transactivation function of HIF-1α by suppressing the dissociation of HIF-1α from FIH-1 and reduced the amount of FIH-1 to co-activator p300. Additionally, Kang et al. [37] demonstrated that FIH-1 promoted pVHL binding to HIF-1α via acetylation by hydroxylating hARD 1/NAA10, a component of *N*-terminal acetyltransferase, under normoxia. However, under low oxygen conditions, the hydroxylation of HIF-1α and the activity of PHD enzymes are inhibited, which caused the HIF-1α subunit to become stable and rapidly accumulate in the cytoplasm [38]. Then, the accumulated HIF-1α translocates to the nucleus, dimerizes with HIF-1β, and recognizes hypoxia response elements (HREs) of the promoters of target genes [39]. The accumulation of HIF-1α leads to the activation of genes involved in angiogenesis, glycolysis, and wound healing. Chen et al. [40] reported that HIF-1α induced by bone morphologic protein 9 (BMP9) significantly promoted the angiogenesis of hepatocellular carcinoma by activating vascular endothelial growth factor A (VEGFA) expression. Gao et al. [41] found that HIF-1α accelerated the process of diabetic wound healing via keratinocyte migration. Overall, the regulation of HIF-1α degradation and synthesis in response to oxygen levels is crucial for cellular homeostasis and adaptation to changing environmental conditions.

Previous studies have demonstrated that constant hypoxia existed inside of keloid tissue [42,43]. Meanwhile, HIF-1α overexpression was observed in keloid tissue [44–46]. Increasing studies showed have shown the roles of HIF-1α in keloid formation [47–50]. This review mainly illustrated the major function of HIF-1α in keloid formation and provided a new perspective on keloid prevention and treatment.

3. Data sources and searches

Four electronic databases, i.e., MEDLINE (PubMed), the EMBASE, Cochrane Library databases, and Google Scholar, were systematically searched to find the eligible studies. The timeframe spanned from the inception of the four databases to March 15, 2023. Only those studies published by utilizing the English language were included. The following search terms used in different combinations in the MEDLINE database were: (HIF1α), (hypoxia), AND (keloid). In addition, the reference lists were manually searched for screening the further eligible studies. The features of the included studies were listed in Table 1, showing the characteristics of and the main findings of the included studies.

Table 1
The features of the included studies.

Study/ Reference	Research subject	Associated genes/ pathways	Measurement	Main findings
Deschene et al. [17] 2012	Horse	NA	Western blotting	Hypoxia promoted the expression of ECM-associated proteins (COL1A1 and MMP2) via inducing HIF-1α in equine dermal fibroblast, leading to scar formation.
Wang et al. [22] 2020	KFs	NA	Western blotting	Hypoxia-inducible HIF-1α promoted proliferation, migration and collagen synthesis and suppressed apoptosis by regulating glucose metabolism in KFs.
Kang et al. [23] 2020	KFs	NA	Western blotting and immunohistochemistry	HIF-1α promoted collagen secretion in KFs.
Jusman et al. [24] 2019	KFs	NA	qRT-PCR and ELISA	HIF-1α induced fibroblast proliferation by promoting Cygb expression in keloids.
Zhang et al. [44] 2023	Keloid tissue samples	NA	Western blotting and immunohistochemistry	Expression levels of HIF-1α showed higher expression in keloid tissue.
Li et al. [45] 2022	Patients	NA	Western blotting and immunohistochemistry	The relative expression of HIF-1α was significantly increased in the recurred keloid skin after radiotherapy.
Si et al. [46] 2020	KFs	NA	Western blotting and qRT-PCR	Resveratrol treated keloids by suppressing proliferation and promoting apoptosis in KFs through the inhibition of HIF-1α.
Liu et al. [47] 2019	Keloid tissue samples and KFs	NA	Western blotting	Ascorbic acid inhibited scar formation by decreasing HIF-1α expression.
Zhang et al. [48] 2018	Keloid tissue samples	NA	Western blotting. qRT-PCR and fluorescence staining	HBOT ameliorated the EMT phenomenon and decreased the invasive ability of keloid keratinocytes by suppressing HIF-1α expression.
Wulandari et al. [49] 2016	Keloid tissue samples	NA	qRT-PCR and ELISA	HIF-1α induced keloid formation by regulating procollagen I and III secretion in KFs.
Zhang et al. [50] 2003	Keloid tissue samples and KFs	NA	Western blotting	The inhibition of HIF-1α deterred scar fibrosis by downregulating PAI-1 gene expression in KFs.
Xu et al. [51] 2018	Keloid tissue samples and KFs	HIF-1α/TGF-β1/Smad	Western blotting, qRT-PCR and immunohistochemistry	Hypoxia promoted collagen deposition by activating TGF-β1/Smad signaling via HIF-1α, leading to the formation of keloids.
Lin et al. [52] 2020	Keloid tissue samples and KFs	HIF-1α and TGF-β/Smad	Western blotting and immunofluorescence	Sumoylation enhanced the activity of the HIF-1α and TGF-β/Smad signaling pathways in keloids.
Lei et al. [53] 2019	Keloid tissue samples and KFs	Parkin/HIF-1α/TGF-β/Smad	Western blotting, qRT-PCR and immunofluorescence	Silencing Parkin significantly enhanced KFs proliferation and inhibited apoptosis by targeting TGF-β/Smad signaling pathway through inducing HIF-1α expression.
Zhao et al. [54] 2017	Keloid tissue samples and KFs	HIF-1α/TGF-β1/Smad3	Western blotting and qRT-PCR	HIF-1α drove the transition of human dermal fibroblasts into myofibroblasts by activating the TGF-β1/Smad3 pathway.
Lei et al. [55] 2019	KFs and male nude mice	HIF-1α/TGF-β/Smad and TLR4/MyD88/NF-κB pathways	Western blotting and immunohistochemistry	The inhibition of HIF-1α significantly inhibited the growth of keloids by suppressing the TGF-β/Smad and TLR4/MyD88/NF-κB pathways.
Lee et al. [56] 2022	KFs	IL-17-STAT3- HIF-1α	Western blotting and immunohistochemistry	The IL-17-STAT3-HIF-1a axis increased necroptosis and fibrosis by causing defective autophagy in KFs.
Kim et al. [57] 2019	Keloid tissue samples and KFs	HIF-1α/ERK/MAPK	Western blotting and qRT-PCR	HIF-1α resulted in abnormal cutaneous scarring by inducing abnormal fibroblast activity through activation of the ERK signaling pathway.
Wang et al. [58] 2022	Keloid tissue samples and KFs	HIF-1α/HOXC6/ERK	Western blotting	HIF-1α promoted proliferation, migration and ECM production in KFs through the HOXC6/ERK signaling pathway, contributed to the progression of keloids.
Zhang et al. [59] 2006	Keloid tissue samples and KFs	ERK1/2/HIF-1α and PI3K/AKT/HIF-1α	Western blotting and immunohistochemistry	The activated ERK1/2 and PI3K/AKT contributed to the accumulation of HIF-1α and the expression of VEGF in KFs. (VEGF)
Syed et al. [60] 2013	Keloid tissue samples and KFs	PI3K/AKT/mTOR/HIF-1α	High-throughput In-Cell Western Blotting	Inhibition of PI3K/AKT/mTOR signaling suppressed keloid cell spreading, proliferation and migration by decreasing the expression of HIF-1α.
Zhang et al. [61] 2014	Keloid tissue samples and KFs	HIF-1α/αvβ3 integrin-PI3K/AKT	Western blotting	HIF-1α stimulated proliferation, collagen synthesis, migration and invasion of KFs by activating αvβ3 integrin-PI3K/AKT signaling pathway through increasing periostin expression.
Zhang et al. [62] 2004	Keloid tissue samples and KFs	ERK1/2/HIF-1α, PI3K/AKT/HIF-1α, and PTKs/HIF-1α	Northern and western blotting analysis	ERK1/2, PI3K/AKT, and PTKs might promote keloid formation by inducing PAI-1 expression through the activation of HIF-1α.

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Table 1 (*continued*)

Study/ Reference	Research subject	Associated genes/ pathways	Measurement	Main findings
Wang et al. [63] 2023	Keloid tissue samples and KFs	PI3K/AKT/HIF-1α	Western blotting	PI3K/AKT pathway promoted KFs proliferation via enhancing glycolysis through interacting with HIF-1α under hypoxia.
Ma et al. [64] 2015	Keloid tissue samples and KFs	NA	Immunohistochemistry, fluorescence staining and western blotting	HIF-1α promoted the transition of keloid-derived keratinocytes into KFs by inducing EMT.
Lei et al. [65] 2019	Keloid tissue samples and KFs	HIF-1α/PKM2	Western blotting and qRT-PCR	Metformin inhibited EMT of KFs via the HIF-1α/PKM2 signaling pathway.
Song et al. [66] 2018	Keloid tissue samples	NA	Immunohistochemistry	HBOT reduced the recurrence rate of keloids by inhibiting HIF-1α and reducing the inflammatory reaction.
Long et al. [67] 2016	Keloid tissue samples and KFs	NA	Western blotting and qRT-PCR	2ME2 significantly increased radiation-induced apoptosis of KFs by inhibiting the protein expression of HIF-1α.

Note: HIF-α = Hypoxia-inducible factor-1α; KFs = Keloid fibroblasts; TGF-β = Transforming growth factor-beta; TLR4 = Toll-like receptor 4; MyD88 = The adaptor protein myeloid differentiation factor 88; NF-κB=Nuclear factor-kappa B; IL-17 = interleukin-17; STAT3 = Signal transducer and activator of transcription 3; AKT = Protein kinase B; Cygb = Cytoglobin; HOXC6=Homeobox C6; ERK = Extracellular regulated protein kinase; PI3K=Phosphoinositide 3-kinase; AKT = Protein kinase B; EMT = Epithelial-to-mesenchymal transition; PKM2 = Pyruvate kinase M2; 2ME2 = 2-methoxyestradiol; HBOT=Hyperbaric oxygen therapy; PAI-1 = plasminogen activator inhibitor-1; PTKs = Protein tyrosine kinases; EMT = Epithelial-to-mesenchymal transition; mTOR = Mammalian target of rapamycin.

4. The roles of HIF-1α in keloids formation

4.1. HIF-1α induced keloid formation by increasing collagen deposition and fibroblast proliferation through by activating the TGF-β/Smad signaling pathway

As we all known, Fibroblast proliferation and ECM synthesis played play important roles in keloid formation [68]. HIF-1 has been reported to promote fibroblast proliferation and ECM synthesis by up-regulating connective tissue growth factor (CTGF), leading to the formation of keloids [69]. Also, Transforming growth factor-β (TGF-β) has been demonstrated to induce sustained fibrosis by cooperating with CTGF [70]. TGF-β, a multifunctional cytokine, comprises three different subtypes (TGF-β1, TGF-β2, TGF-β3) in mammals, activating a heteromeric complex mediated by two types of transmembrane serine/threonine kinase receptors [71]. After the binding of TGF-β, the type II (TβRII) receptor phosphorylates and activates the type I (TβRI) receptor, activating the TGF-β/Smad signaling pathway [72]. The TGF-β/Smad pathway plays a crucial role in cell proliferation, differentiation, and apoptosis [73]. Li et al. [74] found that the expression level of TGF-β was up-regulated in cancer cells during hypoxia.

In addition, TGF-β has been found to be involved in the process of keloid formation by stimulating collagen formation and ECM synthesis [75]. Wang et al. [76] reported that activating transcription factor 3 (ATF3), an adaptive responsive gene, significantly promoted growth and invasion, and inhibited apoptosis by activating the TGF-β/Smad pathway in keloid fibroblasts. Huang et al. [77] demonstrated that HIF-1α drived drove glucose metabolic reprogramming by switching the functionality of the TGF-β/Smad pathway in non-small cell lung cancer. Recently, Xu et al. [51] reported that hypoxia not only promoted TGF-β1/Smad signaling but also elevated HIF-1α expression in keloid fibroblasts (KFs). Furthermore, total collagen deposition increased significantly with prolonged hypoxia for KFs [51]. Importantly, HIF-1α silencing dramatically inhibited the TGF-β/Smad pathway and reversed the collagen deposition induced by hypoxia [51]. Moreover, silencing of Smad4 significantly inhibited the gene and protein expression levels of HIF-1α in KFs [51].

The aforementioned results indicate that HIF-1α increased collagen deposition by activating the TGF-β/Smad signaling pathway in dermal fibroblasts. Li et al. [52] found that the inhibition of desumoylation enhanced collagen deposition and fibroblast migration by activating HIF-1α and TGF-β/Smad signaling pathways. Consistent with these results, other investigators have since demonstrated that HIF-1α overexpression significantly enhanced KFs proliferation and inhibited apoptosis by targeting the TGF-β/Smad signaling pathway [53,54]. These results demonstrated that HIF-1α promoted keloid formation by enhancing collagen deposition and fibroblast proliferation through the activation of the TGF-β/Smad pathway.

4.2. HIF-1α promoted the keloid development by activating TLR4/myd88/NF-κb signaling pathways

Angiogenesis is closely associated with keloid formation because of due to the persistence of inflammation [78]. The inhibition of the TLR4/NF-κB signaling pathway enhanced angiogenesis [79]. Toll-like receptor 4 (TLR4), a transmembrane protein, is widely expresses expressed in inflammatory cells, fibroblasts, and keratinocytes [80]. It binds to endogenous ligands, such as fibronectin and heat shock proteins, and to exogenous one ones, such as lipopolysaccharide [81]. Also, TLR4 has been showed to modulate intracellular signaling transduction via the adaptor protein myeloid differentiation factor 88 (MyD88) [82]. Physiologically, TLR4 plays an important role as a biosensor of tissue injury to initiate tissue repair after injury [82]. It was reported that TLR4 expression was elevated in pathologic fibroses, including keloids [83]. Additionally, TLR4 increased TGF-β signaling and fibroblast activation and

proliferation [84]. Ge et al. [85] found that TLR4 significantly increased atrial fibrosis in spontaneously hypertensive rats by upregulating TGF-β expression. In contrary, the silencing of TLR4 significantly downregulated TGF-β to reduce atrial fibrosis in spontaneously hypertensive rats [85]. Chen et al. [86] demonstrated that higher expression of TLR4 promoted scar formation by increasing the expression of TGF-β and collagen through the Smad4 pathway. Furthermore, Shi et al. [87] reported that astragaloside IV, an active compound, prevented acute myocardial infarction by reducing the expression of TLR4, MyD88, and NF-κB p65. However, whether TLR4/MyD88/NF-κB signaling pathway is involved in keloid formation remains largely unclear. Lei et al. [55] found that the expression levels of HIF-1α, TLR4, MyD88, and NF-κB in KFs were significantly upregulated after hypoxic stimulation.

In addition, KFs was were found to secrete the inflammatory factor IL-6 after hypoxic stimulation [55]. The NF-κB blocker pyrrolidine dithiocarbamate (PDTC) significantly inhibited the secretion of IL-6 in KFs, indicating that the production of IL-6 was primarily modulated by the TLR4/MyD88/NF-κB pathway [55]. Interestingly, the expression changes of TLR4, MyD88, and NF-κB induced by hypoxia were reversed by silencing HIF-1α [55]. Moreover, the silence of HIF-1α suppressed the proliferation of KFs and ex-vivo experiments also demonstrated that the HIF-1α inhibitor inhibited the growth of keloid tissues [55]. These studies suggested that HIF-1α promoted the keloid formation through the activation of the TLR4/MyD88/NF-κB signaling pathway.

4.3. The inhibition of the IL-17-STAT3-HIF-1α axis inhibited keloid formation by suppressing defective autophagy in KF

The fibrotic response is a major mechanism of keloid formation. However, the fibrotic response is the consequence of chronic inflammation in keloids and blocks scar maturation [88]. Various pro-inflammatory cytokines, including IL-4, IL-13, IL-6, and IL-17, play important roles in keloid formation by inducing excessive ECM deposition in association with paracrine signals or autocrine signals arising from fibroblasts [89,90]. Periostin, an ECM protein that plays an important role in skin development, is also involved in a wide range of skin disorders such as abnormal scar formation, wound closure, and systemic scleroderma [91–93]. Maeda et al. [94] reported that IL-4 and IL-13 stimulated TGF-β1expression by inducing periostin secretion, which promoted abnormal scar formation. Lee et al. [95] found that IL-17 promoted keloid formation by stimulating the serection secretion of stromal cell-derived factor-1 through the activation of the STAT3 pathway in keloid-derived skin fibroblasts. There is a close link between inflammatory diseases and autophagy. Cong et al. [96] reported that IL-17 exacerbated fine particulate matter-mediated lung inflammation and fibrosis by suppressing PI3K/Akt/mTOR-mediated autophagy. In addition, IL-17 has been reported to augment the expression of HIF-1α and osteoclast-mediated bone erosion under hypoxia-mimetic conditions [97]. HIF-1α can drives hypoxia-induced autophagy by promoting ATG2A and ATG14 translation [98]. A study from by Liu et al. [99] showed that photodynamic therapy (PDT) promoted keloid-derived fibroblast death by inducing autophagy through SIRT3/SOD2 pathway.

Recently, Lee et al. [56]demonstrated that the expression of IL-17, STAT3, HIF-1α, and p62 were significantly increased in keloid tissue. Furthermore, the number of autophagolysosomes was decreased in KFs compared with that in normal fibroblasts, suggesting that KFs have defective autophagy [56]. Importantly, STAT3 inhibitor (STA21) significantly decreased the expression of HIF-1α, indicating that STAT3 was crucial for the expression of HIF-1α in KFs [56]. Notably, IL-17 increased the expression of p62, STAT3, and HIF-1α and promoted fibrosis in KFs [56]. Meanwhile, the HIF-1α inhibitor decreased the level of p62 and suppressed the fibrosis induced by IL-17, indicating that the inhibition of HIF-1α alleviates defective autophagy in KFs and inhibited keloid formation [56]. These studies showed that the IL-17-STAT3-HIF-1α axis promoted keloid formation by inducing defective autophagy in KFs, suggesting that targeting the axis might have therapeutic potential for keloids.

4.4. HIF-1α-induced HOXC6 promoted keloid formation by activating ERK/MAPK signaling pathway

We have mentioned that TGF-β1 is closely associated with tissue fibrosis and related diseases, including keloids. The extracellular signal-regulated kinase (ERK), a part of the mitogen-activated protein kinase (MAPK) signaling pathway, has been reported to be aberrantly activated in tissue fibrosis and modulate fibroblast differentiation [100,101]. For instance, Cucurbitacin E, a triterpenoid compound, induces apoptosis of activated hepatic stellate cells and ameliorates thioacetamide-induced hepatic fibrosis by activating ERK/MAPK signaling pathway [102]. Interestingly, the activation of the ERK/MAPK signaling pathway was enhanced in keloid fibroblasts, indicating that ERK/MAPK signaling pathway was involved in the procession of keloids [103].

A recent study showed that levels of phosphorylation of ERK and p38 peaked at 8 h after hypoxia exposure [57]. Moreover, the expression levels of HIF-1α and I collagen were increased after 48 h of hypoxia in KFs compared with normal human dermal fibroblasts [57]. Further study found that ERK inhibition suppressed the levels of MMP-2,9 and TIMP-1 induced by hypoxia and reduced the transcriptional level of I collagen type I by 38.3% in hypoxic normal human dermal fibroblasts [57].

In addition, Homeobox C6 (HOXC6), a potential biomarker for the diagnosis and prognosis of tumors, has been demonstrated to promote the proliferation and migration of glioblastoma cells through the activation of the ERK/MAPK signaling pathway [104]. However, whether HIF-1α regulates keloids formation via HOXC6/ERK/MAPK pathway is not yet unclear whether HOXC6/ERK/-MAPK pathway being involved in the action of HIF-1α in keloids formation is not clear. Wang et al. [58] found that HOXC6 gene expression was most altered in microarray datasets from GEO and downregulation of HOXC6 significantly suppressed proliferation, migration, and ECM accumulation and promoted apoptosis in KFs. Furthermore, three binding sites for HIF-1α were found within the promoter region of HOXC6 through the JASPAR database [58]. Also, the dual-luciferase reporter assay showed that HIF-1α enhanced the expression level of HOXC6 and increased the promoter activity (luciferase activity) of HOXC6, indicating that HIF-1α acted the upstream of HOXC6 in KFs [58]. Additionally, the ERK/MAPK pathway is predicted to act the downstream of HOXC6 in KFs by a transcriptome sequencing experiment and a series of bioinformatics analyses [58]. Moreover, silencing of HIF-1α remarkably decreased the expression levels of the HIF-1α, HOXC6, and *p*-ERK compared with the normal group [58]. The researchers have also

found that HOXC6 knockdown inhibited the expression levels of the *p*-ERK and HOXC6 proteins and ERK1/2 inhibitor reduced level of the collagen I in KFs [58]. These studies demonstrated that HIF-1α promoted the development of keloids by increasing the expression of HOXC6 through ERK/MAPK signaling pathway.

4.5. PI3K/AKT pathway promoted keloid formation by modulating angiogenesis, ECM formation, and glycolysis through activating HIF-1α

It is generally assumed that keloid pathogenesis entails collagen synthesis and dysregulated angiogenesis [105]. The PI3K/AKT pathway has been demonstrated to be closely related to collagen synthesis and angiogenesis [106]. The PI3K/AKT pathway, a primary growth regulatory pathway in mammalian cells, plays a major role in multiple cellular processes, including proliferation invasion and apoptosis [107]. Zhu et al. [108] reported that celastrol, a Chinese herbal medicine, significantly suppressed the growth, migration, and invasion of glioblastoma cells by inhibiting angiogenesis through by blocking the activity of the PI3K/AKT/mTOR pathway. Hu et al. [109] found that the PI3K/AKT/mTOR pathway induced pulmonary fibrosis by enhancing the aerobic glycolysis, and promoting collagen synthesis. However, these phenomena could be reversed by mTOR inhibitor or PI3K/AKT inhibitor [109]. Zhang et al. [59] demonstrated that hypoxia induced the expression of VEGF, AKT, and HIF-1α, and pretreatment with PI3K/AKT inhibitor suppressed VEGF expression and blocked the HIF-1α protein accumulation in a dose-dependent manner. In addition, PI3K/AKT/mTOR inhibitor also reduced the expression of HIF1-α [60]. Meanwhile, PI3K/AKT/mTOR inhibitor downregulated ECM, reduced angiogenesis, and decreased fibroblast proliferation in a concentration-dependent manner [60].

Further study found that periostin could stimulated stimulate proliferation, collagen synthesis, migration, and invasion of KFs by activating the αvβ3 integrin-PI3K/AKT signaling pathway [61]. The expression of periostin has been showed to be regulated by HIF-1α [110]. The tissue-type and the urokinase-type plasminogen activators is are involved in ECM formation and their activities are regulated by plasminogen activator inhibitors (PAIs) [111]. The PI3K/AKT signaling pathway has been reported to induce PAI-1 expression by activating HIF-1α, and then promoted promoting keloid formation [62]. Recently, the enhanced glycolysis has also been showed shown to promote keloid formation [112]. Wang et al. [63] showed decreased levels of HIF-1α and glycolysis when KFs were treated with PI3K/AKT inhibitor. Additionally, the phosphorylation of the PI3K/AKT signaling pathway was dramatically suppressed when HIF-1α was inhibited in KFs, indicating that PI3K/AKT pathway might promoted promote keloids formation by enhancing glycolysis through the interaction with HIF-1α [63]. Taken together, PI3K/AKT signaling pathway is involved in keloid formation by regulating angiogenesis, ECM formation, and glycolysis through targeting HIF-1α.

4.6. Metformin might inhibit keloid growth by suppressing hypoxia-induced EMT through the inhibition of HIF-1α/P70S6K1/PKM2 pathway

The keloid formation is closely associated with ECM accumulation. Extensive research has demonstrated that epithelial-to-mesenchymal transition (EMT) promotes fibrogenesis by inducing ECM accumulation in a wide range of tumors [113]. The EMT is a process associated with the loss of epithelial cell polarity and their development into mesenchymal cells with migratory and invasive behavior [114]. During EMT, the expression of *E*-cadherin and zonula occludens-1 (ZO-1), the epithelial markers, are is decreased [115]. Moreover, the expression of vimentin and fibronectin, the mesenchymal markers, are increased, thus leading to nonpolar mobilizable cells [116]. The EMT has been reported to be ubiquitous in organ fibrosis and wound healing [117,118]. Wang et al. [119] found that black phosphorus nanosheets (BPNSs), a new EMT-inducing system integrates, promoted burn wound healing by inducing EMT of epithelial cells through the Snail1-mediated signaling pathway. Recently, the change in the EMT was observed in the keloid tissues [120]. Li et al. [121] demonstrated that hypoxia-induced HIF-1α expression significantly promoted neurogenic bladder fibrosis through inducing EMT.

Although the prominence of hypoxia-induced HIF-1α in the EMT process of neurogenic bladder fibrosis and tumor are is known, their functions in modulating keloid pathological processes remain unclear. Ma et al. [64] reported that the basement membrane area of keloid specimens exhibited high expression of HIF-1α, vimentin, and fibronectin. In addition, *E*-cadherin showed a slightly decreased expression at the same location [64]. Accompanied by the increase in HIF-1α expression, the expression of vimentin and fibronectin were was increased while the expression of ZO-1 was suppressed in keratinocytes in a hypoxic environment [64]. Similarly, the changes in HIF-1α, *E*-cadherin, ZO-1, vimentin, and fibronectin expression were also observed in keloid-derived keratinocytes under hypoxic culture conditions [64]. Meanwhile, the hypoxia-stimulated keratinocytes showed a spindle-shaped similar morphology, resembling fibroblasts [64].

The dermis accumulates excessive amounts of extracellular matrix, resulting in keloids. The pathobiology of keloid formation has been gradually revealed recently. MicroRNAs and lncRNAs can construct pairs of competing endogenous RNA networks, contributing to keloid formation by regulating gene expression, transcriptional modifications, and histone modifications [122]. A recent study demonstrated that Schwann cells contributed to keloid formation by cross-talking with macrophages [123]. In contrast to normal scars, in keloids, the number of Schwann cells was elevated. Besides, the gene expression profile of Schwann cells is distinctly different between keloids and normal skin [123,124]. More recently, single-cell RNA sequencing technology has brought data-driven innovation to elucidate the pathogenesis of keloids [125]. Consequently, the pathological mechanisms of keloid formation may be gradually discovered. At present, various treatments are available for keloids, including conservative approaches (i.e., silicone-based products), physical therapy, mini-invasive treatment (i.e., laser), and highly invasive approaches (i.e., surgical excision with adjuvant brachytherapy) [126]. The selection of keloid treatment mainly depends on the morphology, extensions, and location of the keloid. Moreover, previous therapeutic methods, patient's complaints, and other patient-related characteristics [127]. Typically, keloids consist of proliferating fibroblasts and excessive amounts of extracellular matrix components (mainly collagen), which may induce a

locally hypoxic microenvironment [128]. Under hypoxia, HIF-1α may accumulate in keloids, leading to the overactivation of the fibrotic signaling pathway and causing aggravated fibrosis [128]. As a result, a better understanding of the role of HIF-1α in the pathogenicity of keloids may facilitate to explore new therapeutic approaches.

Further study found that the silencing of HIF-1α significantly decreased the expression of vimentin and fibronectin and increased the expression of *E*-cadherin and ZO-1 in keloid keratinocytes under hypoxic conditions, which suggested the importance of HIF-1α in keloid keratinocytes [64]. The cellular morphology of the keratinocytes was reversed back to an epithelial-like shape via silencing HIF-1α [64]. The above studies indicate that HIF-1α might promote keloid growth by inducing EMT of KFs. However, the specific mechanism of HIF-1α regulating EMT was unrevealed.

The pyruvate kinase M2 (PKM2) has been reported to be a key downstream effector of the HIF-1α and plays an important role in tumor growth. Cheng et al. [129] found that metformin, a typical antidiabetic drug, abolished EMT of cervical carcinoma cells by suppressing PKM2 expression through d inhibiting mTOR/phosphorylation of the p70 ribosomal S6 kinase 1 (P70S6K1) signaling. It was reported that stimulation by hypoxia upregulated the expression of PKM2 and increased the phosphorylation of p70s6k in KFs [65]. Additionally, PKM2 knockdown significantly reduced the HIF-1α-induced gain of vimentin and loss of *E*-cadherin in KFs under hypoxic conditions [65]. More importantly, metformin decreased the expression of HIF-1α, decreased reduced the expression of *E*-cadherin, and rescued the accumulation of vimentin in KFs under hypoxic conditions [65]. Based on these results, metformin might inhibit keloid formation by suppressing hypoxia-induced EMT through HIF-1α/P70S6K1/PKM2 pathway.

Table 1 showed the features of the included studies. The potential molecular mechanisms underlying the roles of the HIF-α pathway in keloids development were illustrated in Fig. 1.

5. Directions for future research

The treatment of keloids is a challenging problem for clinicians and researchers. Based on the evidence obtained from above mentioned aforementioned studies, HIF-1α is one of the critical factors on in keloid formation, which may be associated with the acceleration of proliferation of KFs, enhancement of angiogenesis, and increased deposition of collagen. Therefore, targeting HIF-1α might be potentially served as a therapeutic strategy. For instance, in vitro and in vivo studies showed that 2-methoxyestradiol (2ME2), Metformin and Hyperbaric oxygen therapy (HBOT) could inhibit keloid formation by suppressing the expression of HIF-1α [65–67]. However, there are few studies on the exact effects of HIF-1α on keloid illnesses in clinical practice presently. In future studies, numerous clinical trials are needed to validate the effect of HIF-1α on keloids, which may pave the way for its clinical applications. Since keloids are closely associated with various physical and psychological symptoms, further translational research is warranted to bridge the gap between preclinical findings and clinical applications in the field of keloid treatment.

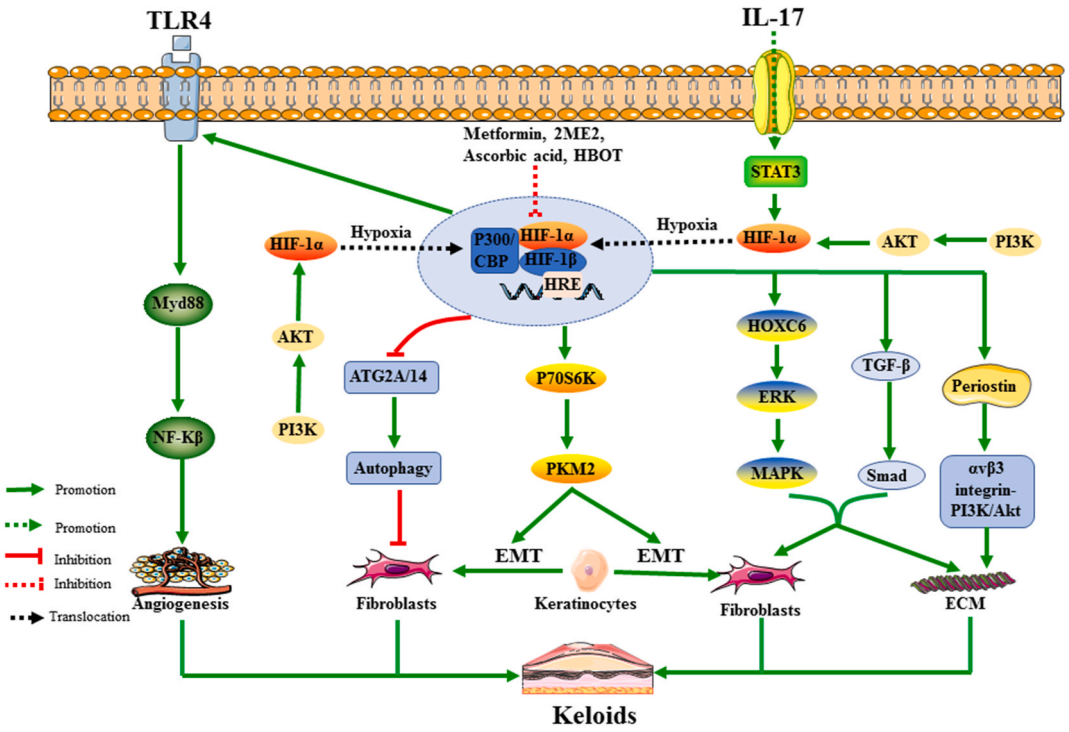

Fig. 1. Molecular mechanisms underlying the roles of HIF-α pathway in keloids development.

6. Conclusion

HIF-1α, a transcription factor under hypoxia, plays crucial roles in various biological processes, including angiogenesis, apoptosis, autophagy, and glucose metabolism. Some previous studies showed that HIF-1α played an important role in keloids. Therefore, the regulation of HIF-1α activity is a breakthrough point in keloid treatment. Up-regulation of HIF-1α can promote the proliferation of KFs, increase the deposition of collagen, and enhance angiogenesis in hypoxic tissues. By contrast, the inhibition of HIF-1α can decrease the proliferation of KFs, reduce deposition of collagen, and prevent angiogenesis. At present, most hypoxia-inducible factor inhibitors are widely studied in solid tumors. We believe that with the in-depth study on the transcriptional mechanism of HIF-1α, some new HIF-1α inhibitors are developed in the future for clinical research, opening a new direction for keloid treatment.

Author contributions

Yuncheng Tai, Liying Zheng, Jiao Liao, and Zixiong Wang conceived the study and drafted the article. Lai Zhang finalized the paper and provided suggestions to improve it.

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Data availability statement

Data will be made available on request.

Conflict of interest declaration

The authors declare no conflict of interest.

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