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Review

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Review

Advances in the pathogenesis and clinical application prospects of tumor biomolecules in keloid

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Abstract

Keloid scarring is a kind of pathological healing manifestation after skin injury and possesses various tumor properties, such as the Warburg effect, epithelial–mesenchymal transition (EMT), expression imbalances of apoptosis-related genes and the presence of stem cells. Abnormal expression of tumor signatures is critical to the initiation and operation of these effects. Although previous experimental studies have recognized the potential value of a single or several tumor biomolecules in keloids, a comprehensive evaluation system for multiple tumor signatures in keloid scarring is still lacking. This paper aims to summarize tumor biomolecules in keloids from the perspectives of liquid biopsy, genetics, proteomics and epigenetics and to investigate their mechanisms of action and feasibility from bench to bedside. Liquid biopsy is suitable for the early screening of people with keloids due to its noninvasive and accurate performance. Epigenetic biomarkers do not require changes in the gene sequence and their reversibility and tissue specificity make them ideal therapeutic targets. Nonetheless, given the ethnic specificity and genetic predisposition of keloids, more large-sample multicenter studies are indispensable for determining the prevalence of these signatures and for establishing diagnostic criteria and therapeutic efficacy estimations based on these molecules.

Key words: Tumor signatures, Keloid, Proteome, Epigenetics, Exosomes, Tumor biomolecules, Biomarkers

Highlights

- Keloid scarring is a kind of pathological healing manifestation after skin injury and possesses various tumor properties.
- Liquid biopsy has the potential to screen for people with keloids due to its non-invasive and accurate properties.
- Epigenetic biomarkers do not require changes in the gene sequence, and their reversibility and tissue specificity make them ideal therapeutic targets.

Background

Keloid disorder is a group of 'tumor-like' pathological scars that grows invasively beyond the injury boundary, with very few spontaneous degenerative changes [1, 2]. Keloid scarring is an unpreventable consequence of trauma, burns, surgery, or no apparent induction, with fibroblast overgrowth and

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excessive collagen secretion as the typical pathological features [3]. The pathogenesis of keloids is intricate and involves the comprehensive effects of multiple factors, such as genetic susceptibility, persistent inflammatory response, endocrine factors and race specificity [4]. Keloids generally occur in areas such as the anterior chest and scapular areas, which are intermittently or continuously in high tension in daily activities [5]. The reason may be that mechanical force signals are converted into chemical signals through mechanically sensitive ion channels and G-protein conjugate receptors on the surfaces of cell membranes, affecting downstream pathways such as transforming growth factor beta (TGF-β)/Smad pathways and tumor necrosis factor alpha (TNF-α)/nuclear factor-kappa B (NF-κB) pathways, thereby stimulating fibroblast proliferation and collagen fiber accumulation [6]. There are numerous keloid treatments, including surgery, radiation therapy and drug injections. Nonetheless, due to the lack of clear biomarkers for the early identification and prevention of keloid scarring, the diagnosis and treatment are relatively immature and can merely be implemented after the formation of keloids [4, 7]. Moreover, the undetermined pathogenesis of keloids leads to the failure of etiological treatment, and the recurrence rate of surgical and nonsurgical symptomatic therapy is high [8].

In recent years, with the increasing understanding of keloids, more scholars have detected the tumor-like properties of keloids, such as the Warburg effect, epithelial–mesenchymal transition (EMT), expression imbalances of apoptosis-related genes and the existence of keloid stem cells [9, 10]. Abnormal expression of tumor signatures in keloids is critical to the initiation and operation of these effects. Under the stimulation of trauma, infection or surgery, some tumor-related factors are activated as dominant modulators or signal molecules, inducing a series of reactions, such as the inflammatory response and accumulation of extracellular matrix [11]. Consequently, they have broad prospects in experimental research and clinical application, including early screening, prevention, assessment of aggressiveness and treatment-response prediction in keloids.

Although the potential value of a single or several tumor signatures in keloids has been acknowledged in many experimental studies [12, 13], it is essential to establish a comprehensive evaluation system that summarizes various tumor signatures in keloids and thoroughly assesses the practicality of these factors in clinical practice. From this perspective, the objective of this article is to summarize the tumor signatures that are abnormally expressed in keloids and to investigate their mechanism of action and their feasibility from bench to bedside (Figure 1).

Review

Signatures in blood and body fluids—liquid biopsy

Clinical pathological sampling is ordinarily undertaken by surgical biopsy or needle biopsy, which is an invasive test. 'Liquid biopsy', as a novel blood test, is easy to perform, and frequent sampling is allowed. Assessing and analyzing circulating cells, DNA and exosomes released from lesions into the blood assist in diagnosing and clarifying the nature of diseases and locating lesions that may metastasize [14, 15]. Burgeoning liquid biopsy is beneficial for keloid prevention and screening as it avoids the skin injury generated by surgical biopsy, and the diagnostic efficiency is notably enhanced [16].

Interestingly, a recent article based on single-cell sequencing and T-cell subtyping identified serum levels of soluble human leukocyte antigen-E (sHLA-E) as a predictive biomarker and potential therapeutic target for keloids. Its sensitivity and specificity could reach 83.69% and 92.16%, which were validated in 104 patients with keloids, 512 healthy donors and 100 patients with an interfering disease. sHLA-E levels decreased following intralesional therapy of keloids with triamcinolone combined with 5-fluorouracil, and monitoring of sHLA-E levels in keloids could be used to determine the recurrence of keloids and guide clinical treatment [17].

Currently, the progression of liquid biopsy in keloids is principally reflected in the investigation of exosomes. Exosomes are derived from polyvesicles formed by intracellular lysosomal microparticle invagination, which transfer signaling molecules such as proteins, DNA and microRNAs (miRNAs) to mediate cell–cell communication and participate in various biological behaviors, including the immune response, cell migration and differentiation [18, 19]. Exosomes are an indispensable link in the process of fibrosis and may serve as a new research direction in the diagnosis and treatment of keloids [20, 21]. Exosomes derived from human endothelial progenitor cells organize fibroblast angiogenesis and mesenchymal–endothelial transformation by transporting miRNA-133 [22]. Exosomes can stimulate the phenotypic differentiation of normal fibroblasts into myofibroblasts that are conducive to invasion and metastasis by TGF-β/Smad signaling pathways [23, 24]. Mechanical stress is able to influence vascular formation by adjusting the secretion of fibroblast exosomes [25].

It is worth noting that the main significance of exosomes for translational medicine is that they serve as ideal non-invasive diagnostic and prognostic markers for personalized monitoring of disease occurrence and progression and as nucleic acid or drug delivery vectors [26]. Exosomes act as vehicles for cell communication, acquiring their contents from their parental cells, and thus exosomes in body fluids may reflect the characteristics, status and disease evolution of their parental cells. For example, glypican 1 can be used to diagnose pancreatic cancer and determine its stage with 100% sensitivity and specificity [27]. For keloids, exosomes contain signaling molecules that are transported to distant sites to regulate the microenvironment of the fibrosis process. Therefore, monitoring the secretion of specific exosomes is expected to provide early screening for patients with keloids. For example, fibroblasts in keloids secrete significantly more exosomal miRNA-21 than normal skin tissue [28, 29]; thus, the evaluation of exosomes containing specific signaling molecules may aid in differentiating keloids from normal skin tissue.

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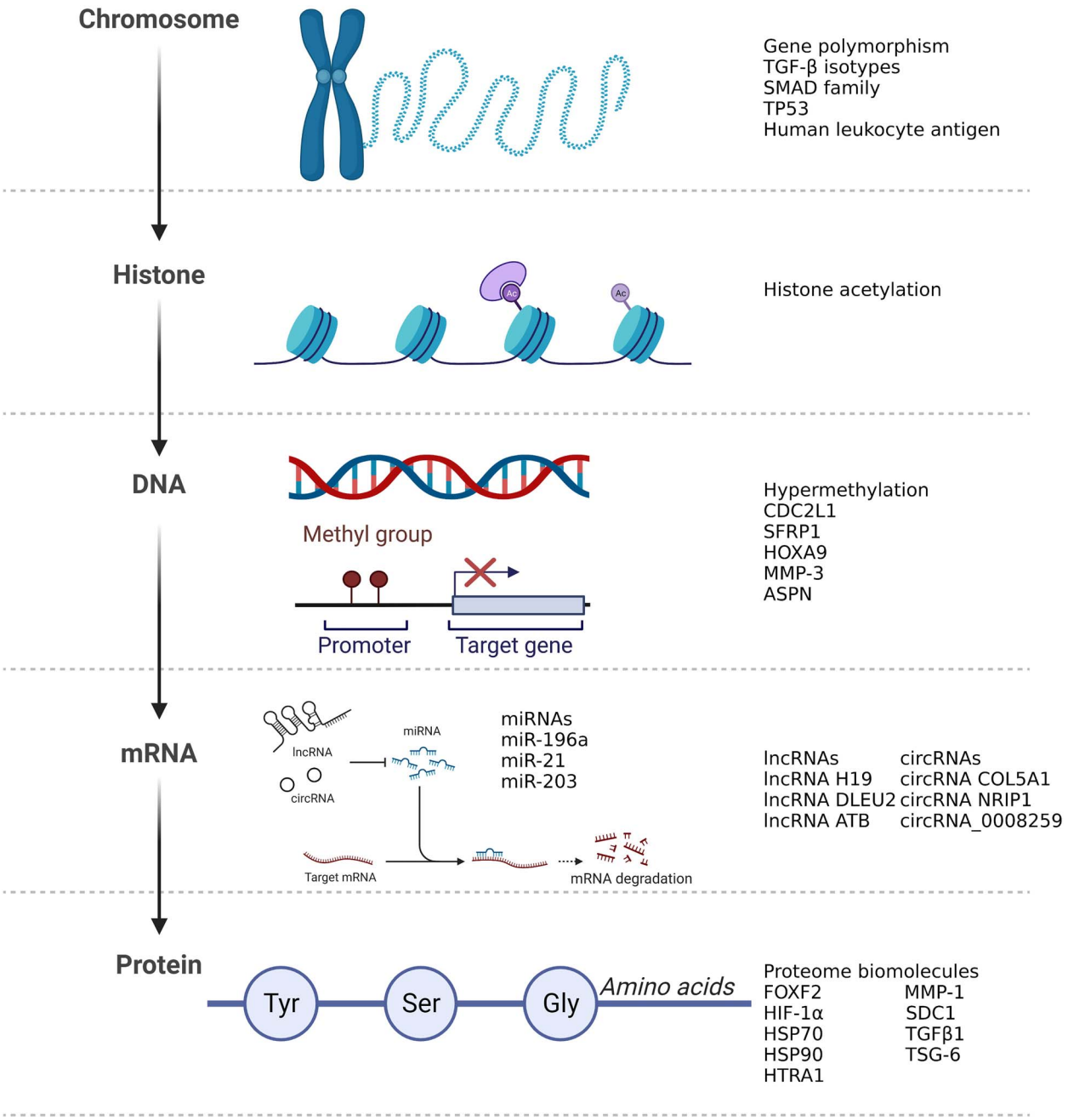

Figure 1. Illustrations of tumor-associated molecules, giving examples of how these molecules may be involved in gene expression from chromosomes to proteins in keloids. Created with BioRender.com. *TGF-β* transforming growth factor beta, *miRNAs* microRNAs, *MMP* matrix metalloproteinase, *ASPN* asporin, *HSP* heat shock protein, *HIF-1α* hypoxia inducible factor 1 subunit alpha, *IL* interleukin, *VEGF* vascular endothelial growth factor

Due to their excellent biocompatibility, low immunogenicity, first-class membrane permeability and penetration, exosomes have incomparable advantages over artificial drug delivery carriers such as liposomes or lipid-based nanoparticles as nucleic acid or drug delivery carriers [30]. In the treatment of keloids, exosomes secreted by mesenchymal stromal cells are capable of inhibiting inflammation and scar formation in the process of wound healing [31]. Autologous transdermal injection of exosomes derived from fibroblasts regulated the expression of procollagen type I and matrix metalloproteinase 1 (MMP-1) and impacted dermal collagen deposition and degradation [32]. Therefore, inducing specific exosomes or constructing drug vectors based on exosomes to intervene in the process of fibrosis and scar formation may be a new direction for the development of new keloid drugs.

Genetic signatures

The first study concentrating on keloid susceptibility sites came from Marneros *et al.*'s genome-wide linkage survey of two keloid families (Japanese and African–American) [33].

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Genetic predisposition to keloids in the Japanese family was linked to locus D2S1399 on chromosome 2q23, a locus that controls the encoding of TNF-α-induced protein 6 (TNFAIP6). Keloid tendency in the African–American family was found to be linked to locus D7S499 on chromosome 7p11, which encodes epidermal growth factor receptor (EGFR). EFGR is exceptionally widely expressed in ovarian cancer and lung adenocarcinoma, is the focal point of targeted therapy and clinical molecular detection [34] and its expression has been substantiated to be significantly higher in keloids than in normal skin tissue [35].

Regarding gene polymorphisms, previous studies have chiefly investigated TGF-β isotypes (TGF-β1, TGF-β2, TGF-β3), members of the SMAD family (SMAD3, SMAD6, SMAD7), mutations in p53 and human leukocyte antigen (HLA) in keloids [36–38]. In an analysis of p53 gene mutations in keloids, mutations were observed in all keloid samples along with increased cell proliferation and an imbalance in apoptosis that was not observed in other normal skin tissues of the same patients [39]. In another study involving 15 keloid samples, mutations in exons of the p53 gene were discovered in all keloid samples [40]. In addition, the importance of the HLA haplotype in the process of keloid fibrosis has been verified in relevant studies [41]. In studies on the association between the HLA system and keloids, the risk of keloid development in Caucasians was positively correlated with the frequency of the HLA-DRB1$*$15 phenotype, and the distribution of HLA-DQA1 and DQB1 alleles was enormously disparate between keloid and normal populations in the analysis of Chinese Han keloid patients [42, 43].

Proteome signatures

Maintaining proliferation To date, the abnormal expression of one or several tumor biomolecules and their functions in keloids (Table 1) have been reported in several studies, including proliferation, apoptosis, extracellular matrix (ECM) deposition, angiogenesis, inflammatory response and EMT (Figure 2). In signaling fibroblast division and differentiation, keloids are considerably different from normal skin tissues in the silencing or downregulation of apoptotic factors, oncogene activation, and the regulation of classical signaling pathways and stress proteins [44–46].

In studies of multiple apoptosis-related factors in keloids, the expression levels of TRADD, TSG-6 and NIP3, which are participants of programmed cell death and apoptosis, were downregulated [47]. Immunohistochemical staining of keloids revealed strong staining of the oncogenes cMYC and Bcl-2 (negative regulators of programmed cell death), negative staining of TP53 (a negative regulator of cell proliferation), and positive staining for the transcription factors c-Jun and c-Fos, which activate protooncogenes and facilitate sustained fibroblast proliferation signals [48–50]. β-Catenin, Wnt5α and Wnt10α are activated, and their expression levels are positively connected with fibroblast proliferation through the classical Wnt/β-catenin signaling pathway [51–54]. HTRA1, a member of the serine protease family induced by heat shock, has the ability to recognize misfolded proteins and degrade a variety of substrates, including ECM [55]. Due to the protease activity of HTRA1, it has been confirmed to be involved in autophagy, apoptosis and the metastasis of malignant tumors. Active keloid lesions express more HTRA1 than normal skin and boost keloid formation during wound healing by involving the cell proliferation process and specific remodeling of the extracellular matrix. Knockdown of HTRA1 in keloid inhibits keloid cell proliferation and exogenous supplementation of HTRA1 in culture medium counteracts this process. [56].

Deposition of ECM Histologically, keloids microscopically present as spiral collagenous fibers, dense collagenous nodules accumulated by fibroblasts and collagenous fibers, diffuse microvascular injury and degeneration or necrosis of fibroblasts [57]. Excessive collagen deposition, or fibrosis, is another focus of research into the pathological mechanisms of keloids [58]. Proteins that regulate the process of fibrosis are primarily concentrated in three groups, namely, cytokines involved in the inflammatory response, components that constitute the extracellular matrix and collagen-processing proteins [59–62].

The cytokine interleukin 6 (IL-6) has been reported to be conducive to the occurrence of a variety of diseases with fibrotic processes, such as scleroderma, cardiac hyperplasia and pulmonary fibrosis [63]. The expression of IL-6 stimulates the synthesis of type I collagen by inducing inflammatory responses and mediating the TGF-β/Smad pathway [64]. Defects in IL-6 delay the re-epithelialization of wound healing and inhibit MMP expression [60, 65]. Activation of MMPs is associated with the invasion ability of various malignant tumors [66]. The roles of MMP-1 and MMP-2 involve accelerating the lysis of ECM and the remodeling of collagen bundles, intensifying the migration ability of fibroblasts and creating conditions for the migration of fibroblasts to the surrounding normal skin [67, 68]. S100, a protein secreted by keratinocytes in inflammatory diseases such as bronchitis and rheumatoid arthritis, has been verified to be down-regulated in keloids. In S100A7- and S100A15-treated fibroblasts, the expression levels of TGF-β subtype molecules, type I collagen, type III collagen and fibronectin-1 decreased [69].

Periostin is expressed in the dermis and basement membrane during embryonic development and is gradually degraded after birth [70]. Nevertheless, in keloids, periostin is upregulated and regulates the fibrosis process and keratinocyte proliferation and is involved in maintaining the mechanical properties of keloids [71]. Osteopontin (OPN), a noncollagenous bone matrix protein, is predominantly involved in the proliferation of fibroblasts and the occurrence and metastasis of epithelial-derived tumors [72]. The expression of OPN in various cells is low under physiological conditions, whereas OPN positivity in the epidermis and

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Table 1. Tumor-associated protein biomolecules differentially expressed in keloids

Biomolecules	Abbreviation	Involved physiological function	Expression in keloids	Associated biological processes in keloids	Reference
Proliferation and apoptosis					
Catenin (Cadherin-associated protein), beta 1	β-Catenin	Cell growth Cell adhesion	Up-regulated	Maintenance of skin fibrosis	[51, 52, 54]
B-Cell lymphoma-2	BCL2	Programmed cell death	Positive in keratinocytes and fibroblasts	Blocked fibroblast apoptosis	[48]
Proto-oncogene C-Fos	C-FOS	Transactivating factor	Positive in dermal fibroblasts	Regulation of fibroblast proliferation	[48]
Calcitonin gene-related peptide	CGRP	Vasodilation	Up-regulated	Gene expression of growth factors in fibroblasts	[46]
c-Myc transcription factor	cMYC	Cell cycle progression Cellular transformation Apoptosis	Down-regulated	Apoptosis	[47]
Proto-oncogene C-Jun	C-JUN	Transactivating factor	Positive in dermal fibroblasts	Regulation of fibroblast proliferation	[48]
Defender against cell death 1	DAD-1	Programmed cell death	Down-regulated	Apoptosis	[47]
Nineteen Kd interacting protein-3	NIP3	Pro-apoptotic factor	Down-regulated	Apoptosis	[47]
Tumor protein P53	TP53	Cell cycle arrest DNA repair Senescence	Down-regulated	Decreased fibroblast proliferation	[48, 50]
Tumor protein P63	TP63	Maintenance of epithelial self-renewal	Up-regulated	Blockade of TP53 activity	[50]
Tumor necrosis factor receptor type 1-associated death domain protein	TRADD	Programmed cell death	Down-regulated	Apoptosis	[47]
Wingless-type MMTV integration site family, member 5A	Wnt5A	Proliferation Apoptosis Differentiation	Up-regulated	Proliferation of fibroblasts	[52]
Wingless-type MMTV integration site family, member 10A	Wnt10A	Proliferation Apoptosis Differentiation	Up-regulated	Proliferation of keloid progenitor cells	[53]
Collagen deposition and extracellular matrix formation					
Collagen type I alpha 1 chain	COLIα1	Type I collagen synthesis	Up-regulated	Collagen synthesis	[71]
Heat shock protein 27	HSP27	Correct folding of proteins	Up-regulated	Matrix synthesis	[76]
Heat shock protein 47	HSP47	Collagen biosynthesis	Up-regulated	Synthesis and secretion of collagen	[76]
Interleukin 6	IL-6	Inflammation Maturation of B cells	Up-regulated	Increased accumulation of ECM Regulation of fibroblast migration Regulation of matrix metalloproteinase function	[60, 65]
Integrin subunit alpha 2	ITGα2	Modulation of collagenase gene expression Organization of newly synthesized ECM	Up-regulated	Matrix synthesis	[46]

(Continued)

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Table 1. Continued.

Biomolecules	Abbreviation	Involved physiological function	Expression in keloids	Associated biological processes in keloids	Reference
Matrix metalloproteinase 2	MMP-2	Cleaving components of the ECM Cleaving molecules involved in signal transduction	Up-regulated	Remodeling of collagen bundle regions Degradation of ECM	[67, 68]
Matrix metalloproteinase 13	MMP-13	Breakdown of ECM	Up-regulated	Remodeling of the extracellular matrix Immune response	[66]
Matrix metalloproteinase 19	MMP-19	Breakdown of ECM	Up-regulated	Remodeling of the extracellular matrix Chronic inflammation	[46]
Osteopontin	OPN	Cell adhesion Signal transduction	Up-regulated	Collagen synthesis Fibroproliferation	[73]
Periostin	POSTN	Tissue development Regeneration	Up-regulated	Collagen synthesis Proliferation of KFB Migration of KFB Invasion of KFB	[71]
S100 Calcium binding protein	S100	Cell cycle progression Cell differentiation	Down-regulated	ECM production	[69]
Thymic stromal lymphopoietin	TSLP	Immune response Inflammatory response	Up-regulated	Increased collagen I and collagen III expression	[58]
Inflammatory response					
Chemokine-like factor 1	CKLF-1	Immune surveillance Inflammation response	Up-regulated	Inflammatory response	[60]
C-X-C Motif chemokine receptor 4	CXCR4	Regulation of cell migration Inflammatory response	Up-regulated	Inflammatory response	[59, 60]
C-X-C Motif chemokine ligand 9	CXCL9	Immunoregulatory Inflammation response	Up-regulated	Inflammatory response	[61]
C-X-C Motif chemokine ligand 12	CXCL12	Immune surveillance Inflammation response	Up-regulated	Activation of the inflammatory response	[62]
Interleukin 17	IL-17	Proinflammatory cytokine	Positive	Inflammation Fibrosis	[109, 110]
Angiogenesis					
Interleukin 8	IL-8	Chemotactic factor	Up-regulated	Increased recruitment of endothelial progenitor cells	[80]
Jagged canonical notch ligand 1	JAG1	Fibroblast growth factor-induced angiogenesis	Up-regulated	Angiogenesis Enhanced fibroblast activity	[83]
Vascular endothelial growth factor	VEGF	Angiogenesis Endothelial cell growth	Positive in the basal layer of the epidermis	Angiogenesis	[85, 86]
Platelet-derived growth factor	PDGF	Angiogenesis Cell proliferation Differentiation	Positive	Angiogenesis Fibronectin production	[85]
Endothelial–mesenchymal transition					
Interleukin 18	IL-18	Proinflammatory cytokine	Up-regulated	Epithelial–mesenchymal interaction Increased collagen expression Increased secretion of profibrotic cytokines	[98]

(Continued)

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Table 1. Continued.

Biomolecules	Abbreviation	Involved physiological function	Expression in keloids	Associated biological processes in keloids	Reference
Phosphatase and tensin homolog deleted on chromosome ten	PTEN	Tumor suppressor	Positive in keloid keratinocytes	EMT transition	[99, 100]
Signal transducer and activator of transcription 3	STAT3	Cell growth Apoptosis	Up-regulated	Epithelial–mesenchymal interaction Cell proliferation Collagen production	[101]
Wingless-type MMTV integration site family, member 3A	Wnt3A	Regulation of cell fate Patterning during embryogenesis	Up-regulated	EMT transition	[102]
Stem cells in keloids					
Kruppel-like factor 4	KLF4	Differentiation of epithelial cells	Positive in keloid-derived precursor cells	Development of individualized induced pluripotent stem cells from fibroblasts	[107]
Lin-28 homolog	LIN28	Developmental timing	Positive in keloid-derived precursor cells	Development of individualized induced pluripotent stem cells from fibroblasts	[107]
Octamer-binding protein 4	4-Oct	Embryonic development Stem cell pluripotency	Positive in keloid-derived precursor cells	Development of individualized induced pluripotent stem cells from fibroblasts	[107]
Sry-box transcription factor 2	SOX2	Embryonic development Determination of cell fate	Positive in keloid-derived precursor cells	Development of individualized induced pluripotent stem cells from fibroblasts	[107]

KFB keloid fibroblast cells, *EMT* endothelial–mesenchymal transition, *ECM* extracellular matrix

fibroblasts was noted by immunohistochemical staining of keloid [73].

The heat shock protein (HSP) family acts as a molecular chaperone to prevent stress-induced protein aggregation, and multiple HSP molecules have specific abnormal expression profiles in a variety of tumors [74]. For example, HSP27 can be a predictor of the progression of endometrial carcinomas [75]. As the HSP family is involved in the folding and synthesis of collagen in the endoplasmic reticulum, members of the HSP family are markedly increased in keloids and maintain the correct folding of collagen [76]. HSP47 directly or indirectly engages in collagen synthesis and secretion through the TGF-β/Smad pathway or as a molecular chaperone of collagen [77].

Angiogenesis The continuous supply of nutrients is indispensable for tumor proliferation and metastasis. Accordingly, the expression of multiple angiogenesis regulators is associated with the degree of malignancy and the aggressiveness and prognosis of a variety of tumors and this phenomenon is similar in keloids [78, 79]. The cytokine IL-8 has been ascertained to amplify endothelial progenitor cell recruitment in keloids [80], and JAG1 may boost angiogenesis induced by fibroblast growth factor (FGF) through the Notch signaling pathway [81–83]. As the main angiogenic mediators, platelet-derive growth factor (PDGF) and vascular endothelial growth factor (VEGF) are expressed in myofibroblasts, vascular endothelial cells and vascular pericytes in keloids, and maintain the vascular density required for nutrient transport and metabolism by stimulating the proliferation of vascular endothelial cells [84–86]. PDGF synthesized and secreted by fibroblasts may encourage chemotaxis and the division of microvascular smooth muscle cells through paracrine action, which may be the molecular pathological basis of microvascular distortion and hyperplastic occlusion [87, 88]. Disruption of nutrient supply follows hyperplastic occlusion of blood vessels, hinders the regeneration of transitional structures between the dermis and the epidermis, and is ultimately manifested histologically as the loss of dermal papilla, basement membrane and skin appendages [89].

Energy metabolism 3D images of keloids reveal the extensive distribution of occluded microvessels, possibly due to excessive proliferation of endothelial cells protruding into the lumen and compression of surrounding fibroblasts and collagen. The vascular distribution in the center is sparser and the lumen is more flattened, suggesting a more hypoxic environment in the center of the keloid [87, 90]. Moreover, keloid energy metabolism is similar to that of tumors, with much higher lactic acid levels than those of normal skin, sustaining continuous anaerobic glycolysis [91, 92].

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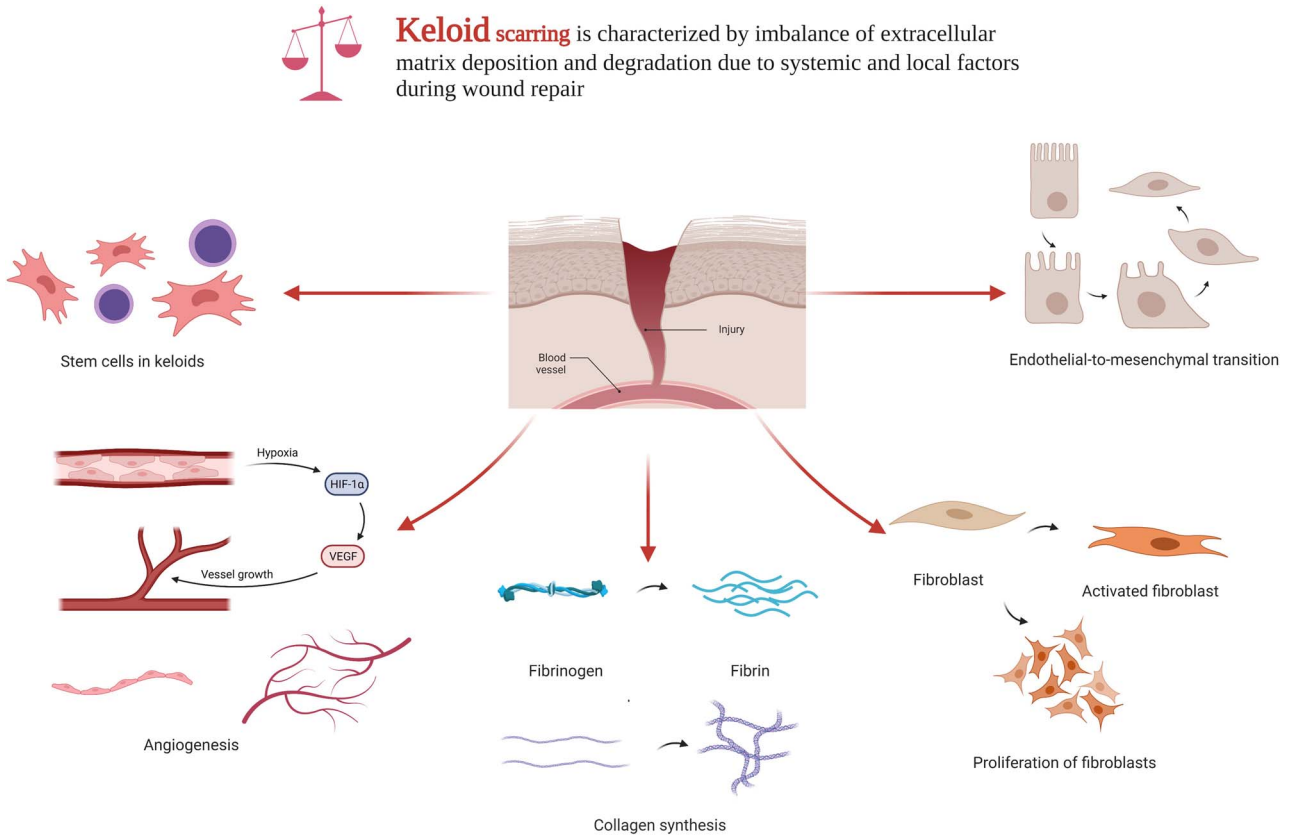

Figure 2. Key pathological processes involved in the development of keloids by proteomic molecules. Created with BioRender.com. *HIF-1α* hypoxia inducible factor 1 subunit alpha, *VEGF* vascular endothelial growth factor

Hypoxia inducible factor 1 (HIF-1) induced under hypoxia promotes the expression of the inflammatory factor IL-6 by activating the TLR4/MYD88/NF-κB pathway [93]. Likewise, it elevates the secretion of connective tissue growth factor and supports the transformation of dermal fibroblasts into myofibroblasts by activating the TGF-β/Smad signaling pathway [94, 95].

EMT transition EMT is a biological process in which epithelial cells undergo biochemical adjustments to acquire a mesenchymal phenotype, forfeit polarity and acquire invasiveness. EMT is ubiquitous and enables cells to achieve higher antiapoptotic competence [96–98]. In keloids, the tumor suppressor phosphatase and tensin homolog (PTEN) and Akt signaling pathways have been reported to participate in keratinocyte and fibroblast phenotypic modifications and the acquisition of stemness [99–101]. Treating human dermis microvascular endothelial cells with Wnt-3α increases the expression of vimentin, a characteristic protein of mesenchymal cells [102]. Activated HIF-1α in hypoxic environments is instrumental in the EMT process and migration capacity of keratinocytes, which can be reversed by hyperbaric oxygen therapy [103, 104].

Stem cells in keloids Fibroblasts from normal skin do not have cloning capability. However, a cloning culture of keloid fibroblasts demonstrated that the self-renewal ability of keloid fibroblasts was much higher than that of normal fibroblasts, and they were able to continuously expand outwards, which might be related to keloid stem cells [105, 106]. Keloid stem cells mostly have two phenotypes: mesenchymal stem cells and hematopoietic stem cells [105, 106].

Immunohistochemical staining of the embryonic stem cell markers OCT4 and SOX2 is positive in keloid-associated lymphoid tissue [107]. OCT4 is a crucial transcription factor in embryonic stem cells that maintains the self-renewal and undifferentiated state of embryonic stem cells by activating pluripotency-related genes and inhibiting the expression of differentiation-related genes [108]. In addition, the increased expression of the IL-17/IL-6 axis in the inflammatory response is partly responsible for the formation of self-renewing and multicompetent derived precursors in keloids [109, 110].

Clinical translation Advances in transcriptomics, proteomics and experimental techniques have facilitated better identification of molecular signatures of keloids and understanding of keloid pathogenesis, and certain biomolecules that have been identified exhibit some potential for clinical application in the scientific translation of proteomics. Bagabir *et al*. revealed strong immunoreactivity of syndecan-1 in the reticular dermis of keloids by immunohistochemical staining, whereas staining was completely absent or slight in hyperplastic scars,

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normal scars, healthy skin and dermatofibrosarcoma protuberans, thus recommending syndecan-1 as a diagnostic marker to differentiate keloids and avoid misdiagnosis of dermatofibrosarcoma protuberans [111]. Syndecan-1, a heparan sulfate proteoglycan, is a principal component of the ECM and mediates cell adhesion and migration. Syndecan-1 on the cell surface restricts cell migration and enhances the binding force between cells and the ECM. The loss of expression of syndecan-1 is a marker of the transformation of epithelial cells into mesenchymal cells [112]. Knockdown of Syndecan-1 resulted in a markedly diminished proliferation of keloid fibroblasts and reduced expression of components of the extracellular matrix [113].

Several biomolecules such as forkhead box F2 (FOXF2), HIF-1α and TSG-6 are expected to be potential targets for keloid treatment (Table 2). Stevenson *et al*. performed transcriptome and metabolome sequencing analysis of keloid promoters and observed significant differences in both methylation and expression of FOXF2 in keloids, and knockdown of the transcriptional regulator FOXF2 significantly suppressed the expression of extracellular matrix-related genes and collagen I production [114]. Keloid fibroblasts treated with inhibitors targeting HSP90 exhibited a dose-dependent reduction in proliferative capacity and cell migration, and a similar phenomenon was observed with interference with HSP70 expression [76, 115, 116]. Tan *et al*. found that the expression level of TSG-6 within keloid lesions was significantly reduced compared to the dermis of normal skin [117], and Li *et al*. induced growth inhibition and G2/M phase block of keloid fibroblasts and activation of the mitochondrial apoptotic pathway by lentiviral transfection of TSG-6 in keloids [118, 119]. Hypoxia triggers HIF-1α protein accumulation and EMT processes in keloids [104, 120]. Hyperbaric oxygen therapy, which increases tissue oxygenation, alleviates the inflammatory process, regulates HIF-1α expression and reduces the recurrence rate of keloids after surgical excision and radiotherapy [121]. 2-Methoxyestradiol, which aims at HIF-1α, assists keloid fibroblasts to increase their sensitivity to radiotherapy [122]. Resveratrol, by targeting HIF-1α, reverses the effects of hypoxia on keloid and induces the onset of apoptosis [123].

Epigenetic signatures

miRNAs Ubiquitously expressed in eukaryotes, miRNAs are a class of endogenous single-stranded RNAs with a length of ~21–23 nucleotides, characterized by fine regulation of oncogenes and their specific expression in tissue [124, 125]. miRNAs (Table 3) have been proven to foster or curb keloid progression by influencing cell proliferation and invasion, EMT processes, ECM deposition and classical signaling pathway transduction [126–138].

Downregulation of miR-199a-5p, miR-203, miR-217, miR-29a, miR-3141 and miR-138-5p and upregulation of miR-181a, miR-31, miR-96 and miR-424-3p are instrumental in the regulation of specific target genes involved in cell cycle regulation and strengthen the viability, proliferation, invasiveness and resistance to apoptosis of fibroblasts or keratinocytes [136, 139–148]. miR-205-5p regulates FOXM1, a transcription activator of cell proliferation, to influence the proliferation, glucose consumption, lactic acid production and other glycolysis processes of fibroblasts and participates in the PI3K/Akt pathway to impede cell migration [149]. Multiple miRNAs, including miR-1224-5p, miR-152-5p and miR-637, have been determined to act on members of the SMAD family and the TGFβ-Smad pathway, thereby manipulating the production of type I collagen, type III collagen and fibronectin, as well as fibroblast-induced vascular production [150–152]. In addition, miR-200c adjusts the expression of the protein-coding gene ZNF217 and controls the autocrine activity of TGF-β2 [153].

Fas ligand (FasL) is expressed on the surface and in the cytoplasm of a variety of tumor cells, and miR-21 has been shown to block mitochondrial-mediated apoptosis by inhibiting FasL activation [154]. miR-21-5p modulates the expression of vimentin in keratinocytes, induces the EMT phenotype and reinforces cell cloning ability and stemness [99]. miR-2392 is vastly downregulated in keloids and has an interaction site with zinc finger E-box binding homeobox 2 (ZEB2); silencing ZEB2 can reverse the effects of the miR-2392 inhibitor on apoptosis, invasion and EMT processes [155].

Long noncoding RNAs (lncRNAs) As a class of RNA molecules longer than 200 nucleotides, lncRNAs are regulatory molecules in biological processes, including gene expression, gene imprinting, cell division, cell differentiation and plasmatic nuclear transfer [156, 157]. lncRNAs can be employed as *cis*- or *trans*-regulators to regulate histone modification, chromatin remodeling and RNA metabolism at the epigenetic level [158]. High-throughput sequencing of tumor tissues and normal tissues shows that abnormal expression of various lncRNAs is closely linked to the occurrence and development of tumors [159, 160]. lncRNAs may be involved in almost all human cancers, and their expression is correlated with the prognosis and metastasis of tumors. Additionally, the secondary structure established by the combination of lncRNAs and specific proteins is anticipated to be an important means to intervene in tumor occurrence and growth [161].

lncRNA DLEU2, lncRNA H19 and lncRNA LINC01116 have been described to act as specific miRNA sponges (Table 4), promoting the proliferation of fibroblasts and enhancing cell migration [136, 162, 163]. lncRNA LINC00937 hinders cell proliferation by the miR-28-5p/MC1R axis in keloids, and its expression is inhibited in fibroblasts [164]. lncRNA HOXA11-AS is upregulated in keloids, and miR-124-3p, as its downstream effector molecule, engages in TGFβR1-mediated angiogenesis and SMAD5-mediated collagen synthesis [165, 166]. lncRNA HOXA11-AS has been demonstrated to support the proliferation of fibroblasts and glycolysis through the miR-205-5p/FOXM1 axis [149]. The expression of lncRNA ATB is positively

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Table 2. Potential proteomic biomarkers in keloids

Biomarker	Abbreviation	Involved physiological function	Expression in keloids	Associated biological processes in keloids	Role in keloids	Reference
Forkhead Box F2	FOXF2	Cell proliferation Cell invasion	Up-regulated	Maintenance of extracellular matrix-related gene expression	Involvement in the pathogenesis of keloids Potential therapeutic target	[114]
Hypoxia inducible factor 1 subunit alpha	HIF-1α	Energy metabolism Angiogenesis	Up-regulated	Metabolic adaptation to hypoxia	Involvement in the pathogenesis of keloids	[93, 120]
Heat shock protein 70	HSP70	Correct folding of proteins	Up-regulated	HSP70 knockdown decreases collagen production in KFB	Potential therapeutic target	[76, 115]
Heat shock protein 90	HSP90	Cell cycle control Signal transduction	Up-regulated	Regulation of apoptosis, proliferation and migration of fibroblasts Heat shock protein 90 inhibitor induces apoptosis and reduces cell migration in keloid fibroblasts	Potential therapeutic target	[116]
High-temperature requirement A serine peptidase 1	HTRA1	Cell growth	Up-regulated	Acceleration of cell proliferation Remodeling of keloid-specific ECM	Involvement in the pathogenesis of keloids	[56]
Matrix metalloproteinase 1	MMP-1	Breakdown of ECM	Up-regulated	Regulation of fibroblast migration Regulation of matrix metalloproteinase function	Involvement in the pathogenesis of keloids	[68]
Syndecan-1	SDC1	Cell binding Cell signaling Cytoskeletal organization	Up-regulated	Matrix synthesis	Potential molecular diagnostic biomarker	[111, 113]
Transforming growth factor β-1	TGF-β1	Cell growth Cell differentiation	Up-regulated	Collagen synthesis Fibroproliferation	Involvement in the pathogenesis of keloids	[38, 71]
TNF-α-stimulated Gene-6	TSG-6	ECM stability Cell migration	Down-regulated	Induction of apoptosis in KFB Remodeling of the extracellular matrix Inflammation	Potential therapeutic target	[117–119]

KFB keloid fibroblast cells, *EMT* endothelial–mesenchymal transition, *ECM* extracellular matrix

associated with the self-secretion level of TGF-β2, which is accomplished by downregulating tumor-suppressive miR-200c and subsequently acting on zinc finger protein 217 (ZNF217), an agitator associated with TGF-β [153]. In keloid RNA sequencing and miRNA sequencing, a total of 319 lncRNAs were identified, and two pairs of competing endogenous RNA networks regulating the actin cytoskeleton were constructed: lnc-GLB1L-1/miR-370-3p/EGFR and lnc-CASP9–3/miR-204/ITGB5 [167].

Almost all of these lncRNAs with abnormal expression in keloids have been extensively scrutinized in tumors, and their mechanisms have been confirmed in multiple cancers [160,

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Table 3. Abnormal expression and biological processes of tumor-associated microRNAs in keloids

miRNA	miRNA expression	Potential value	Target genes	Main associated tumors	References
miR-1-3p	Down-regulated	Induced cell apoptosis Suppression of proliferation and migration	TM4SF1	Oral squamous cell carcinoma Prostate cancer	[126]
miR-1224-5p	Down-regulated	Suppressed cell proliferation, migration and invasion	SMAD3	Rectal cancer Lung cancer	[150]
miR-124-3p	Down-regulated	Promoted cell apoptosis Inhibited fibroblast-induced angiogenesis Inhibited proliferation and migration	TGF-βR1 SMAD5	Prostate cancer Gastric cancer Colorectal cancer	[165, 166]
miR-133a-3p	Down-regulated	Inhibited fibrosis and proliferation	IRF5	Colorectal cancer Prostate cancer	[127]
miR-138-5p	Down-regulated	Induced cell apoptosis	CDK6	Colorectal cancer Breast cancer	[143]
miR-141-3p	Down-regulated	Induced cell apoptosis Suppression of proliferation and migration	GAB1	Rectal cancer Renal cell carcinoma	[128]
miR-152-3p	Up-regulated	Increased cell proliferation and invasion Increased type I collagen, type III collagen and fibronectin production	FOXF1	Colorectal cancer Prostate cancer	[129]
miR-152-5p	Down-regulated	Inhibited proliferation Reduced migration Promoted apoptosis	SMAD3	Liver cancer Gastric cancer	[151]
miR-181a	Up-regulated	Inhibited apoptosis Enhanced keloid fibroblast DNA synthesis and proliferation	PHLPP2	Lung cancer Ovarian cancer	[142]
miR-188-5p	Down-regulated	Inhibited cell proliferation Suppressed DNA synthesis Suppression of migration and invasion	MMP-2 MMP-9	Breast cancer Gastric cancer	[130]
miR-194-3p	Down-regulated	Inhibited proliferation and migration	RUNX2	Breast cancer	[131]
miR-194-5p	Down-regulated	Inhibited the aggressive phenotypes of keloid fibroblasts	NR2F2	Pancreatic cancer Colorectal cancer	[132]
miR-196a	Down-regulated	Inhibited expression of type I and III collagens	COLIα1 COLIIIα3	Pancreatic cancer Breast cancer	[133]
miR-196b-5p	Down-regulated	Suppressed cell viability, migration and extracellular matrix production	FGF2	Non-small cell lung cancer Breast cancer	[134]
miR-199a-5p	Down-regulated	Regulation of cell cycle Restrained proliferation	N/A	Thyroid cancer Lung cancer	[139]
miR-200c	Down-regulated	Suppressed autocrine secretion of TGF-β2	ZNF217	Ovarian cancer Breast cancer	[153]
miR-203	Down-regulated	Induced apoptosis Suppressed proliferation, migration, invasion and ECM production	SMAD5 EGR1 FGF2	Prostate cancer Ovarian cancer	[135, 136]
miR-204	Down-regulated	N/A	ITGβ5	Gastric cancer Hepatocellular cancer	[167]
miR-205	Down-regulated	Induced cell apoptosis Suppression of proliferation and invasion	N/A	Thyroid cancer Cervical cancer	[168]
miR-205-5p	Down-regulated	Inhibited glycolysis Accelerated apoptosis Inhibited proliferation, migration, invasion and ECM accumulation	FOXM1 VEGF	Endometrial cancer Breast cancer	[149]
miR-21	Up-regulated	Inhibited activation of the caspase-8 egulation of mitochondria-mediated apoptotic signaling pathway Promoted cell proliferation Promoted fibrosis	FasL SMAD7 PTEN	Colon cancer Lung cancer	[28, 29, 154]
miR-214-5p	Down-regulated	Induced cell apoptosis Suppression of proliferation and migration	TM4SF1	Esophageal cancer Prostate cancer	[126]
miR-21-5p	Up-regulated	Stemness Epithelial–mesenchymal transition	PTEN	Gastric cancer Lung cancer	[99]

(Continued)

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Table 3. Continued

miRNA	miRNA expression	Potential value	Target genes	Main associated tumors	References
miR-217	Down-regulated	Inhibited cell proliferation Induced apoptosis	FN	Prostate cancer Colon cancer	[144]
miR-2392	Down-regulated	Regulation of epithelial–mesenchymal transition and autophagy	ZEB2	Gastric cancer	[155]
miR-28-5p	Up-regulated	Promoted ECM deposition and cell proliferation	MC1R	Prostate cancer Colorectal cancer	[164]
miR-29a	Down-regulated	Inhibited viability, proliferation, migration and invasion	COLIα1	Cervical cancer Breast cancer	[145]
miR-30a-5p	Down-regulated	Induced cell apoptosis	BCL2	Colon cancer Ewing tumor	[12]
miR-31	Up-regulated	Regulation of cell cycle Restrained apoptosis	HIF-1α	Lung cancer Breast cancer	[141]
miR-3141	Down-regulated	Suppressed keloid fibroblast proliferation and migration Promoted cell apoptosis	SAMD3	Osteosarcoma	[146]
miR-370-3p	Up-regulated	N/A	EGFR	Melanoma Breast cancer	[167]
miR-424-3p	Up-regulated	Enhanced the ability of cell proliferation, migration and collagen secretion Reduced apoptosis	SMAD7	Ovarian cancer	[147]
miR-4328	Down-regulated	Induced cell apoptosis Suppressed proliferation and metastasis	BCL2	Lung cancer	[137]
miR-4417	Down-regulated	Induced cell apoptosis Suppression of migration and invasion	CCND1	Prostate cancer Triple-negative breast cancer	[138]
miR-637	Down-regulated	Suppressed proliferation and metastasis	SMAD3	Breast cancer Prostate cancer	[152]
miR-7-5p	Down-regulated	Repressed proliferation, migration and extracellular matrix deposition Promoted cell apoptosis	EPAC1	Thyroid cancer Glioma	[171]
miR-769-5p	Down-regulated	Inhibited proliferation, migration and invasion Suppressed extracellular matrix deposition	EIF3A	Pancreatic cancer Prostate cancer	[163]
miR-96	Up-regulated	Increased type I and III collagen production	SMAD7	Breast cancer Urothelial carcinoma	[148]

N/A not available, *miR* microRNA,*TM4SF1* transmembrane 4 L six family member 1, *SMAD3* SMAD family member 3, *TGF-βR1* transforming growth factor beta receptor 1, *IRF5* interferon regulatory factor 5, *CDK6* cyclin-dependent kinase 6, *GAB1* growth factor receptor-bound protein 2-associated binding protein 1, *FOXF1* forkhead box F1, *PHLPP2* PH domain and leucine-rich repeat protein phosphatase 2, *MMP-2* matrix metallopeptidase 2, *RUNX2* RUNX family transcription factor 2, *NR2F2* nuclear receptor subfamily 2 group F member 2, *COLIα1* collagen type I alpha 1 chain, *FGF2* fibroblast growth factor 2, *ZNF217* zinc finger protein 217, *EGR1* early growth response 1, *ITGβ5* integrin subunit beta 5, *VEGF* vascular endothelial growth factor, *FasL* Fas ligand, *PTEN* phosphatase and tensin homolog, *FN* fibronectin, *ZEB2* zinc finger E-box binding homeobox 2, *MC1R* melanocortin 1 receptor, *BCL2* B-cell lymphoma-2, *HIF-1α* hypoxia inducible factor 1 subunit alpha inhibitor, *EGFR* epidermal growth factor receptor, *CCND1* cyclinD1, *EPAC1* exchange protein directly activated by CAMP 1, *EIF3A* eukaryotic translation Initiation factor 3 subunit A

161, 168]. It should be acknowledged that there is still a large number of lncRNAs identified in tumors or fibrotic diseases that have not been evaluated in keloids. Furthermore, some lncRNAs have prognostic and diagnostic value in tumors [160, 161], although there is still a lack of relevant studies on whether lncRNAs have similar value in keloids.

Circular RNAs Due to their special 3′ end and 5′ end covalently linked structure, circular RNAs (circRNAs) can act as miRNA sponges and competitively inhibit miRNA binding to target gene mRNAs. circRNAs are expressed in a variety of physiological and pathological processes and have predictive significance for the screening and prognosis of a variety of tumors [169, 170]. Considering the high stability and low off-target ability of circRNAs, the design of artificial sponges aimed at miRNAs in specific diseases is a promising novel future direction for the advancement of targeted drugs.

circRNA_101238 is shown to be involved in the regulation of cyclins as a competitive endogenous RNA [143]. circ-COL5A1 is upregulated in keloids and promotes fibroblast proliferation and collagen synthesis. RNA fluorescence *in situ* hybridization suggested that this effect was accomplished by adjusting the release of Epac1 by circCOL5A1 as a sponge of miR-7-5p [171]. Likewise, circNRIP1 is involved in the proliferation and apoptosis of tumor cells in breast and gastric cancers and is highly expressed in human keloids.

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Table 4. Overview of tumor-associated long non-coding RNAs in keloid scars

lncRNA	lncRNA expression	Potential value	Target miRNA	Main associated tumors	References
lncRNA ATB	Up-regulated	Increased autocrine secretion of TGF-β2	miR-200c	Gastric cancer Colorectal cancer	[153]
lncRNA CACNA1G-AS1	Up-regulated	Promoted proliferation and invasion Suppressed apoptosis	miR-205	Ovarian cancer Colorectal cancer	[168]
lncRNA DLEU2	Up-regulated	Promoted proliferation and differentiation Suppressed apoptosis	miR-30b-5p miR-30a-5p	Pancreatic cancer Lipoma	[162]
lncRNA H19	Up-regulated	Intensified migration and invasion Increased extracellular matrix deposition	miR-769-5p miR-29a	Breast cancer Colorectal cancer	[145, 163]
lncRNA HOXA11-AS	Up-regulated	Promoted fibroblast-induced angiogenesis Promoted glycolysis Inhibited apoptosis Intensified migration and invasion Promoted proliferation and ECM accumulation	miR-205-5p miR-124-3p	Glioma Gastric cancer	[149, 165]
lncRNA LINC00937	Down-regulated	Repressed extracellular matrix deposition Suppressed cell proliferation	miR-28-5p	Cutaneous melanoma	[164]
lncRNA LINC01116	Up-regulated	Intensified migration and invasion Promoted proliferation and ECM accumulation Suppressed apoptosis	miR-203 miR-3141	Prostate cancer	[136, 146]

miR microRNA, *lncRNA* long non-coding RNA, *TGF-β2* transforming growth factor beta 2, *ECM* extracellular matrix

circNRIP1 blocks the ubiquitination of FXR1, a key molecule of miR-503 maturation, by binding to it [172]. The elevation of circNRIP1 is ultimately accompanied by an increase in miR-503, which has been shown to escalate extracellular matrix deposition and promote cell division and differentiation (Table 5).

Studies on circRNAs have been combined with biological information to predict potential functions and screen target miRNAs based on sequence information. A circRNA microarray analysis of keloids identified 76 significantly differentially expressed circRNAs and corresponding specifically bound miRNAs. For instance, circRNA_0043688 may have adsorption effects on miRNA-942-5p, miRNA-3177-3p and miRNA-5010-5p [173]. Until now, there have been few studies on circRNAs in keloids, and further experimental studies are necessary to evaluate circRNA biomolecules that are expected to be utilized in the clinical diagnosis and treatment of keloids [174].

DNA methylation As an essential epigenetic process in eukaryotes, DNA methylation modifies chromatin structure and gene expression by establishing, maintaining and removing methyl groups [175]. Methylation of different components has dissimilar effects on gene expression, and DNA methylation of promoters constrains gene expression. Conversely, high methylation of the silencer is positively related to gene expression. Undisciplined DNA methyltransferase and hypermethylation of normal nonmethylated CpG islands are chief mechanisms of genomic DNA modification to induce tumors [176].

Of the 450,000 cytosine sites scanned in keloids, 37% of differentially methylated genes were hypermethylated, and 63% were hypomethylated, such as MMP3 and asporin [177, 178]. CDC2L1 promoters had a higher methylation rate, up to 50%, compared with 0% in normal skin tissue. This increased methylation rate is associated with a higher fibroblast growth rate and impedes the expression of the apoptosis-related protein cyclin-dependent kinase (CDK)11p58 [179]. Hypermethylation of the secreted frizzled-related protein 1 (SFRP1) promoter in keloids and epigenetic silencing of SFRP1 lead to mitigated inhibition of the Wnt/β-catenin signaling pathway [180], which participates in proliferation, invasion, fibrosis and EMT processes in a variety of tumors and keloids (Table 6).

DNA methylation can be detected directly in blood and body fluids, and diagnostic models based on the methylation levels of multiple genes can accurately and noninvasively screen for tumors [181, 182]. Moreover, due to the reversibility of DNA methylation, the hypothesis of curbing tumor growth by reorganizing the levels of DNA methylation without changing the gene sequence, reactivating tumor suppression genes or silencing oncogenes has been in the experimental stage of intervention in T-cell lymphoma, colon cancer and rectal cancer [183, 184]. Therefore, this approach is expected to become an auxiliary treatment for keloids when they mature.

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Table 5. Tumor-associated circular RNAs abnormally expressed in keloid scars

circRNA	circRNA expression	Potential value	Target miRNAs	Main associated tumors	References
circRNA COL5A1	Up-regulated	Promoted proliferation, migration and ECM deposition Inhibited cell apoptosis	miR-7-5p	Renal Cell Carcinoma	[171]
circRNA NRIP1	Up-regulated	Promoted proliferation Increased expression of ECM-associated proteins Suppressed apoptosis	miR-503-3p miR-503-5p	Lung cancer Gastric cancer	[172]
circRNA_0008259	Down-regulated	Inhibited type I and III collagen expression	N/A	Gastric cancer	[174]

miRNA microRNA, *circRNA* circular RNA, *ECM* extracellular matrix, *N/A* not available

Table 6. Mechanism and clinical value of DNA methylation in keloids

DNA methylation	Alteration	Potential value	Downstream gene or pathway	Main associated tumors	References
CDC2L1	Hypermethylation	Reduced apoptosis	CDK11-p58	Melanoma Neuroblastoma	[179]
SFRP1	Hypermethylation	Increased protein expression of α-SMA	Wnt/β-catenin pathway	Prostate cancer Breast cancer	[180]
HOXA9	Hypermethylation	A component of the tumorigenic phenotype of keloids	N/A	Leukemia Ovarian cancer	[178]
MMP3	Hypomethylation	Promoted proliferation	N/A	Esophageal cancer Melanoma	[178]
ASPN	Hypomethylation	Collagen binding	N/A	Colon cancer Ductal breast carcinoma	[178]

α-SMA alpha-smooth muscle actin, *N/A* not available, *MMP* metalloprotease, *CDC2L1* cell division cycle 2-like 1, *SFRP1* secreted frizzled-related protein 1, *HOXA9* homeobox A9, *ASPN* asporin, *CDK11* cyclin-dependent kinase 11, *N/A* not available

Conclusions

Maturing molecular biology and burgeoning experimental detection technology have promoted the in-depth investigation of the pathological mechanism of keloids. Epigenetic signatures and liquid biopsy may have greater progression potential. Since the former do not require alterations in the gene sequence, their reversibility and tissue specificity make them more ideal therapeutic targets. Liquid biopsy is noninvasive and accurate, it is more suitable for the early screening of people with keloids. It is worth mentioning that serum levels of sHLA-E can be used as a predictive biomarker and potential therapeutic target for keloids due to its high sensitivity and specificity, but considering the ethnic specificity and genetic predisposition of keloids, more large-sample, multicenter studies are needed to determine the prevalence of sHLA-E. In addition, current studies on keloids mostly concentrate on a single molecule. Whether the sensitivity of diagnosis can be upgraded by integrating multiple biomarkers remains to be clarified in future studies.

Abbreviations

CCND1: CyclinD1; CDC2L1: Cell division cycle 2-like 1; CDK11: Cyclin-dependent kinase 11; circRNA: Circular RNA; ECM: Extracellular matrix; EGFR: Epidermal growth factor receptor; EMT: Endothelial–mesenchymal transition; FasL: Fas ligand; FGF2: Fibroblast growth factor 2; FOXF1: Forkhead box F1; HIF1AN: Hypoxia inducible factor 1 subunit alpha inhibitor; HOXA9:Homeobox A9; HSP: Heat shock protein; IL-6: Interleukin 6; MMP-2: Matrix metallopeptidase 2; miRNA: MicroRNA; OPN: Osteopontin; PTEN: Phosphatase and tensin homolog; SFRP1: Secreted frizzled-related protein 1; α-SMA: α-Smooth muscle actin; TGFβ: Transforming growth factor beta; VEGF: Vascular endothelial growth factor; ZEB2: Zinc finger E-box binding homeobox 2; ZNF217: Zinc finger protein 217.

Authors' contributions

XYJ and WYB conceived and wrote the manuscript. SMJ and HY reviewed the manuscript. SMJ, LH and LZY checked the manuscript. HY and CQ provided useful discussions. All authors contributed to the article and approved the submitted version.

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Conflicts of interest

None declared.

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