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Original Article

Noncoding RNAs: emerging players in skin cancers pathogenesis

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Abstract: Skin malignancies form in tissues of the skin and are the most frequent cancers in the world, with an increasing incidence and a steady fatality rate. They are classified as melanoma or nonmelanoma cancers, which include basal cell carcinoma and squamous cell carcinoma. Noncoding RNA transcripts have received increased attention after the thorough analysis of the human genome revealed that most of the genomic components are not encoded to protein. MicroRNAs, long noncoding RNAs, and circular RNAs are some of the well-studied types of these noncoding regions. The alteration in any of these members' expression is associated intrinsically with human cancers, including skin malignancies, due to their critical functions in cell processes for normal development. As a result, investigating the noncoding component of the transcriptome opens up the possibility of discovering new therapeutic and diagnostic targets. This review discusses current studies on the involvement of microRNAs, long noncoding RNAs, and circular RNAs in the pathogenesis of human skin cancers.

Keywords: Skin cancer, microRNA, lncRNA, circRNA

Introduction

Skin cancers are malignancies that arise from the skin and they are mainly divided into two types according to their source of tumor cells. They are non-melanoma skin cancer (NMSC) and melanoma skin cancer [1]. NMSCs originate from epidermal cells, develop in the upper layers of the skin, and are classified into two types, including basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) [2]. BCC is the most common form of skin cancer which is accounts for 75% of cases of NMSC and up to 30% of Caucasians develop BCC at some point in their lives. Indeed, this type of skin cancer grows slowly and only harms the surrounding tissue. BCC scarcely spreads to distant areas or causes death and its metastatic rate is <0.1% [3, 4]. Ultraviolet light, immunodeficiency, having lighter skin which resulted in a higher risk of DNA damage, and chronic arsenic exposure are some of the main risk factors for BCC [5]. It has been revealed that genetic alterations may contribute to the carcinogenesis of BCC. PTCH1 is a key part of the hedgehog signaling pathway, and functions as a tumor suppressor [6]. Studies revealed that the inactivation of PTCH1 is an essential event for BCC pathogenesis. Point mutations and loss of heterozygosity of the PTCH1 are frequently identified in BCC [7]. Other molecular elements and genetic pathways have been identified in BCC tumorgenicity, such as Hippo-YAP signaling, MYCN/FBXW7 signaling, TERT-promoter, TP53, etc. cSCC is the second most common skin cancer after BCC and responsible for about 20% of all skin cancer cases [8].

In contradistinction to BCC, cSCC has a higher risk of distant metastasis and causes 51,900 deaths in 2015 [9]. Sunlight exposure and a reduction of the activation or efficacy of the immune system are the most important risk factors for cSCC [10]. It has been proven that cSCC is one of the malignancies with the highest mutation rate [11]. Around 90% of cSCC cases have inactivation of TP53 in epidermal

keratinocytes which increases UV-induced simple mutations [11]. Mutations in several other genes, such as NOTCH, EGFR, RAS, and CDKN2A are reported in cSCC patients [12].

Melanoma, also known as malignant melanoma, is considered one of the most aggressive and treatment-resistant cancers, caused by the neoplastic transformation of melanocytes [13]. It is estimated that melanoma accounts for 324,635 new cancer cases and more than 57,000 deaths in 2020 [14]. Although surgical removal of the tumor leads to a desirable outcome in the early stages, surgery rarely causes enduring patient survival outcomes in advanced stages of the diseases because of the aggressive behavior and metastatic ability [15]. Exposure to ultraviolet light (UV) is the major cause of melanoma. Furthermore, some genomic mutations are common in melanoma patients, such as mutant BRAF, mutant RAS, mutant NF1, and Triple-wild-type [16]. BRAF is a member of the RAF kinase family which affects cell division through regulating the MAP kinase/ERKs signaling pathway [17]. Several studies show that approximately 70% of melanomas have mutations in the MAPK signaling pathway; moreover, BRAF is mutated in around 50% of the cases, resulted in promoting early oncogenic events of the disease [18]. CDKN2A is one of the most important known genetic factors associated with melanomas and regulates some crucial cell cycle pathways, such as the p53 pathway and the RB1 pathway. The TCGA data reveals that genetic changes in CDKN2A happen in 69% of melanoma cases [16].

According to the statistics, skin cancers are prevalent worldwide. Although many advances have been made in understanding the biology and treatment of skin cancers, there are still many underlying molecular mechanisms that remain to be investigated. Through the past decades, numerous studies indicated the crucial regulatory roles of noncoding RNAs in both developmental processes and various diseases. Undoubtedly, the deregulation of noncoding RNAs is an important feature of cancer [19]. Noncoding RNAs can serve as strong biomarkers for the diagnosis and prognosis of cancers. Moreover, noncoding RNAs can be a potential target for cancer therapy and nucleic acid-based therapeutics have shown success in several preclinical studies targeting noncoding RNAs in cancers. This review aims at discussing the biogenesis and functions of different types of noncoding RNAs. Moreover, we summarize the potential role of noncoding RNAs in skin cancers initiation, promotion, and progression.

Noncoding RNA in cancers

RNAs that do not encode proteins are referred to as noncoding RNAs. Despite noncoding RNAs do not have the ability to encode proteins, they can control the expression of numerous genes via a number of mechanisms. In the last 30 years, noncoding RNAs are becoming more widely considered as critical regulators in both normal cellular function and disease, such as cancer [20, 21].

Traditionally, noncoding RNAs have been divided into two categories: short and long, based on a 200-nucleotide threshold in mature transcript length [22]. MicroRNAs (miRNAs or miRs), small interfering RNAs (siRNAs), small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs), piwi-interacting RNAs (piRNAs), and tRNA derived small RNAs (tsRNAs) are some of the well-known forms of the short noncoding RNAs [23]. Long noncoding RNAs (lncRNAs) are the other group of noncoding RNAs which are divided into subgroups based on where they are located in the genome and their evolutionary background, such as enhancer RNAs (eRNAs), long intergenic noncoding RNAs (lincRNAs), pseudogenes, etc. Recent studies demonstrated that the vast majority of lncRNAs are likely to be functional [22]. They are participating in several cellular and molecular functions, which include gene transcription, post-transcriptional regulation, translation regulation, RNA interference, imprinting, X-chromosome inactivation, chromosome stability, etc. [24]. Circular RNAs (circRNAs) are the emerging type of single-stranded closed circular RNA molecules whose biological function and regulatory role are still not well understood. Recent studies revealed that these circular RNA molecules may serve as promising biomarkers in various human cancers [25].

By playing crucial roles in the regulation of many pathophysiology properties of cancer cells, such as evading apoptosis, angiogenesis, sustained cell proliferation, and drug resistance, noncoding RNAs act as tumor suppressors or oncogenes, and their expression is frequently dysregulated during cancer initiation and development (**Figure 1**). In the next

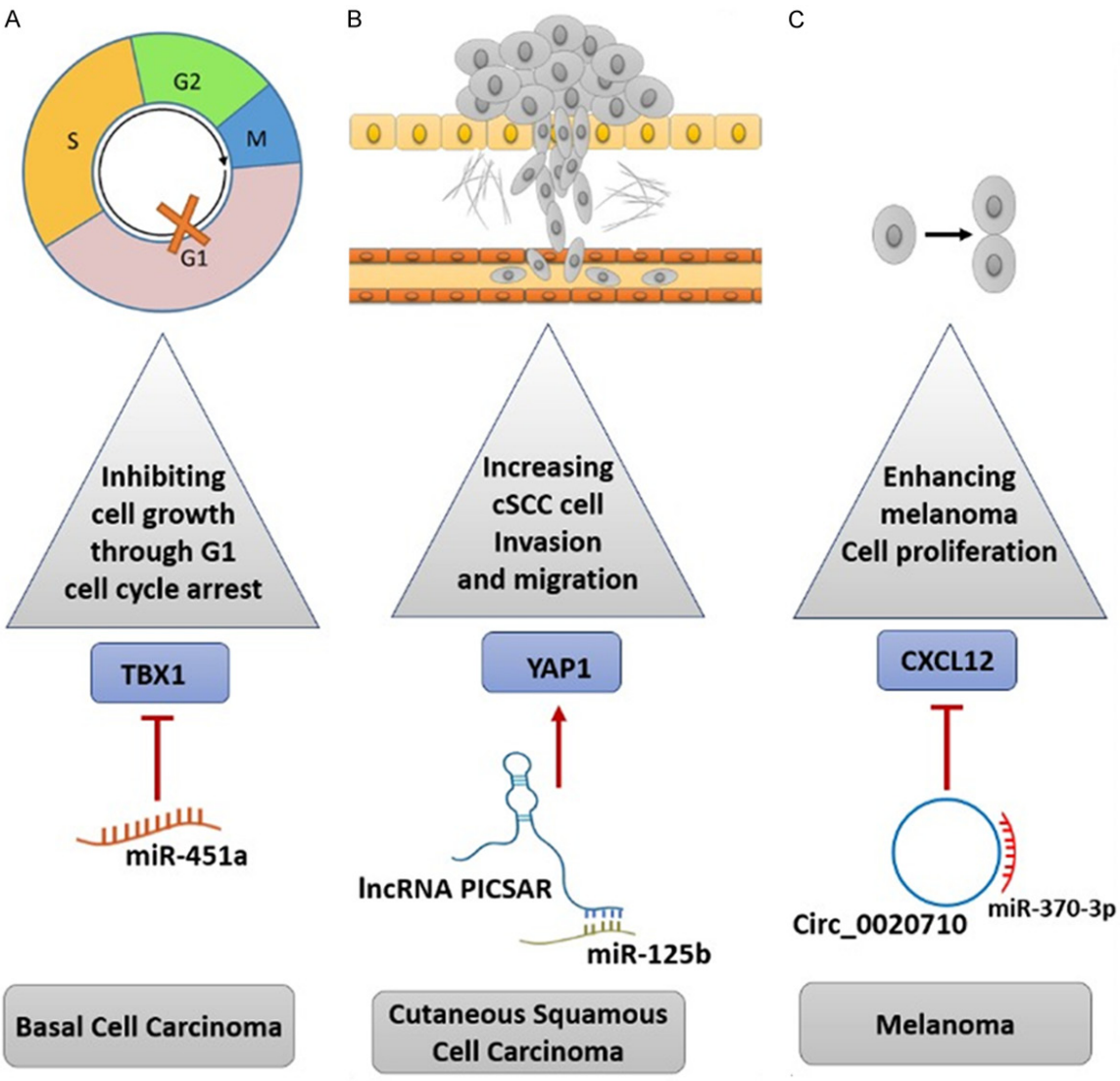

Figure 1. Noncoding RNAs act as major regulators in human skin cancers through regulating some hallmarks of cancer, such as cell migration, invasion, and proliferation. A. MiRNAs can target and suppress many molecules. Considering the functions of their targets, miRNAs are considered either oncogene or tumor suppressor. Ectopic overexpression of miRNA-451a inhibits cell growth by targeting TBX1, causing G1 cell cycle arrest in BCC tumor cells. B. Sponging miRNAs is one of the main forms of regulating gene expression which is done by lncRNAs. LncRNA PICSAR has a high expression level in cSCC cells and tissues. PICSAR promotes the progression of cSCC by sponging miRNA-125b and activating YAP1. C. Unlike to miRNAs and lncRNAs, circRNAs are stable because of their loop structure, which make them a potential biomarker for human cancers. They also have regulatory functions in skin cancers. Circ_0020710 upregulates the expression level of CXCL12 through targeting miRNA-370-3p, which leads to melanoma cell proliferation, migration, and invasion.

sections, we focus on the functions of the some important ncRNAs, including miRNAs, lncRNAs, and circRNAs, which may explain their involvement in skin cancers pathogenicity.

MicroRNAs

MicroRNAs or miRNAs are a group of small noncoding RNAs with a length of about 19-25 nt, which have the ability to target dozens or even hundreds of genes at the same time [26]. They have vital roles in fundamental biological processes [27]. The majority of miRNAs genes are transcribed in the nucleus by RNA polymerase II and III [28]. It has been discovered that miRNAs bind to a particular sequence at the 3'UTR of their target mRNAs to induce translational repression as well as mRNA deadenylation and decapping [29, 30]. The miRNAs profiling has previously been shown to be essential for the

Table 1. The regulatory functions of noncoding RNAs in basal cell carcinoma

Name	ncRNA class	Expression	Function of ncRNA	Ref.
miRNA-451a	miRNA	↧	miRNA-451a/TBX1 axis play a crucial role in BCC tumorigenesis	[39]
miRNA-34a	miRNA	↧	miRNA-34a is a tumor suppressor that could be used as a biomarker	[40]
miRNA-203	miRNA	↧	miRNA-203 and c-JUN regulate basal cell proliferation and differentiation	[41]
miRNA-143-145 clusters	miRNA	↧	tumor-suppressive cluster miRNA-143-145 are downregulated in BCC	[43]
H19	lncRNA	↥	the role of H19 in BCC tumorigenicity is not well understood yet	[73]
CASC15	lncRNA	↥	the role of CASC15 in BCC tumorigenicity is not well understood yet	[73]
SPRY4-IT	lncRNA	↥	the role of SPRY4-IT in BCC tumorigenicity is not well understood yet	[73]
Circ_0005795	circRNA	↥	Circ_0005795 promotes BCC cell proliferation via sponging miRNA-1231	[99]

diagnosis and prognosis of various types of cancers, including skin cancers and some miRs have the potential to be utilized as therapeutic targets in human malignancies [31-37].

Emerging roles of microRNAs in human skin cancers

In the last decade, increasing number of studies have been done on the possible role of miRNAs in human skin malignancies, reflecting the significant interest in the involvement of miRNAs in skin cancer initiation, development, and metastasis (**Table 1**). The capability of miRNAs in the regulation of gene expression is one of the main primary drivers of this interest. Changing levels of only one miRNA expression may alter hundreds of target mRNAs [33]. Several studies reported the aberrant expressions of miRNAs in BCC [38]. The expression level of miRNA-451a is significantly decreased in both human and mouse BCC tissues. Ectopic overexpression of miRNA-451a in BCC tumor cells inhibited cell growth by causing G1 cell cycle arrest. Moreover, inhibiting miRNA451a promoted BCC cell growth and colony formation, validating the tumor suppressor role of this miRNA in BCC [39]. Another recent study found that BCC patients' serum expression of miRNA-34a is considerably lower than that of healthy individuals. The level of miRNA-34a expression in the BCC group was also associated with a worse prognosis [40]. MiRNA-203, which is predominantly expressed in the skin tissue, was found to be downregulated in BCCs. Mechanistically, activation of the Hedgehog pathway suppresses miRNA-203 in BCC. Moreover, it has been proven that the activation of the EGFR/MEK/ERK/JUN signaling pathway may be a potential cause of decreased miRNA-203 expression in BCC [41]. MiRNA-143 and miRNA-145, a cluster located on chromosome 5q32 and have been generally reported as tumor suppressors [42]. It has been shown that miRNA-145-5p is significantly downregulated in BCC [43].

MiRNA-21 is considered one of the most famous oncogenic miRNAs which are upregulated in various types of cancer [44, 45]. Upregulated miRNA-21 mediated PI3K/AKT pathway by regulating TIMP3 in cSCC, resulted in contributing to the disease progression [46]. In the mouse model of cSCC, miRNA-21 inhibition decreased cell growth and slowed tumor growth and metastasis. TIMP3 silencing restored the impact of miRNA-21 downregulation on the progression of cSCC. Furthermore, miRNA-21 depletion decreased activation of PI3K/AKT pathway through modulating TIMP3 in cSCC cells [46]. By regulating ACVR1, miRNA-130a functions as a tumor suppressor and modulates the activity of the BMP/SMAD1 pathway in cSCC [47]. It is reported that overexpression of miRNA-130a decreases long-term growth, cell motility, and invasion ability [47]. Cancer stem cells (CSCs) are a type of tumor cell that can initiate new tumors and induce relapses [48]. These types of stem cells are typically identified and enriched using cell surface markers such as CD44, CD24, CD166, and CD133 [49]. It has been discovered that miRNA-199a-5p is linked to CD44 proteolysis modulation. Overexpression of miRNA-199a-5p decreased cell proliferation and reduced the cSCC CSCs stemness [50]. Mechanistically, miRNA-199a-5p prevented CD44 cell proteolysis, decreased the CD44 domain release and nuclear trans localization through the targeting of Sirt-1. Moreover, the impacts of miRNA-199a-5p overexpression or Sirt1 suppressing turnover by CD44 intracellular domain overexpression, resulted in enhancing the transcriptional expression of Oct4, Sox2, and

Nanog [50]. MiRNA-766 is another oncomiR in cSCC which its upregulation promotes cell proliferation, migration, and invasion [51]. PTEN is a suppressor gene that is commonly inactivated in various types of human cancers [52]. Recent findings indicated that miRNA-221 is a crucial element in the development and progression of tumors [52]. In cSCC cell lines, miRNA-221 increases the cell proliferation and cell cycle through suppressing PTEN [52].

Numerous findings demonstrated the aberrant expression of miRNAs in melanoma. The miRNA-29 family includes three members miRNA-29a, miRNA-29b, and miRNA-29c which are highly conserved across the species [53]. The oncogenes MYBL2 and MAFG are two putative miRNA-29 targets that increase cell proliferation in melanoma. It has been shown that decreasing miRNA-29b2c expression induces melanoma formation, at least partially, by activating MYBL2 and MAFG [53]. KAI1 or CD82 gene is an essential tumor suppression and transcriptional regulator in several kinds of malignancies [54]. By targeting KAI1, miRNA-633 increases melanoma cell proliferation and migration [54]. MiRNA-18a is a member of miRNA-17-92 cluster which is commonly deregulated in human cancers [55]. Recent research found that miRNA-18a is abundantly expressed in melanoma tissues, increasing proliferation while decreasing apoptosis and autophagy in melanoma cells via targeting and suppressing EPHA7 expression [56].

Myc is a family of proto-oncogenes that commonly contributes to tumorigenicity [57]. This group of proteins regulates more than 15% of the entire genome and participates in a variety of biological processes including cell proliferation, differentiation, and immune surveillance [57]. There are a great number of findings indicating the interaction between different miRNAs and MYC in cancer. MiRNA-27b can prohibit the progression of melanoma through targeting MYC [58]. It is proposed that the expression levels of miRNA-27b in melanoma tissue samples are lower than adjacent normal tissues. Ectopic overexpression of miRNA-27b drastically decreased melanoma cell DNA synthesis, vitality, and invasive ability through suppressing MYC [58]. Tumor cells exhibit some molecular and phenotypic changes as cancer progresses, which is referred to as cellular plasticity [59]. Melanoma cell plasticity is one of the primary causes of its ability to spread [60]. Recent research combining mathematical models and experiments demonstrated that miRNA-222 is one of the important factors that controlling melanoma plasticity [61].

FOX proteins are a family of transcription factors that are mutated in various human cancers [62]. There is some evidence that suggests miRNAs can regulate the members of this family in melanoma. For instance, miRNA-1246 promotes melanoma cell viability and metastasis by suppressing FOXA2 [63]. FOXP1 is another member of the FOX family which is regulated by miRNA-92a in melanoma cells [64]. MiRNA-92a is upregulated in melanoma and has been found to be substantially linked with tumor stage and poor prognosis in melanoma patients. By controlling FOXP1, miRNA-92a promotes the malignant development of melanoma [64]. Another study on melanoma demonstrated that miRNA-182 promotes metastasis by targeting FOXO3 [65].

Numerous studies revealed the interactions between miRNAs and RNA-binding proteins (RBPs) in cancers [66]. CSDE1 is an oncogenic RBP that promotes tumorigenicity in various cancers [67]. In melanoma, CSDE1 and AGO2 compete to bind PMEPA1 mRNA, resulting in upregulation of PMEPA1 [68]. Besides, CSDE1 exerts its oncogenic functions by inhibiting miRNA-129-5p-mediated silencing of PMEPA1 in melanoma [68].

According to the mentioned findings, miRNAs can play a dual role in skin cancers pathogenicity. A comprehensive understanding of the roles of miRNAs in the initiation and development of skin malignancies will help us to pave the way for better translation of miRNAs into clinics, establishing them as a potential method in skin cancers treatment.

Long noncoding RNAs

RNA transcripts that are not translated into protein and length more than 200 nucleotides are defined as long noncoding RNAs or lncRNAs [69]. When compared to miRNAs, lncRNAs are more abundant but less conserved during evolution. Although there is still a discussion about the number of functional lncRNAs, it is well documented that an increasing

Table 2. Noncoding RNAs play major role in cutaneous squamous cell carcinoma

Name	ncRNA class	Expression	Function of ncRNA	Ref.
miRNA-21	miRNA	↑	MiRNA-21 promotes cSCC progression by mediating TIMP3/PI3K/AKT signaling axis	[46]
miRNA-130a	miRNA	↓	tumor suppressor miRNA-130a regulates the BMP/SMAD1 pathway by targeting ACVR1	[47]
miRNA-199a-5p	miRNA	↓	MiRNA-199a-5p inhibits cSCC stem cell stemness by targeting Sirt1 and CD44ICD cleavage signals	[50]
miRNA-766	miRNA	↑	miRNA-766 contributes to cSCC tumorigenicity by targeting PDCD5	[51]
miRNA-221	miRNA	↑	The oncogenic miRNA-221 promotes cSCC progression via suppressing PTEN	[52]
miRNA-675	miRNA	↑	H19/miRNA-675 axis can affect EMT-related markers, including E-cadherin, vimentin and N-cadherin, leads to inducing EMT	[78]
miRNA-451a	miRNA	↓	The tumor suppressor miRNA-451a inhibits cell proliferation, migration, invasion, and EMT in cSCC cells	[113]
miRNA-3619-5p	miRNA	↓	MiRNA-3619-5p suppresses cSCC cell proliferation and cisplatin resistance by targeting KPNA4	[124]
PICSAR	lncRNA	↑	PICSAR exerts its oncogenic functions through regulating various pathways, such as miRNA-125b/YAP1 axis and ERK1/2 pathway. Exosomal PICSAR also contributes to cisplatin resistance in cSCC cells through targeting miRNA-485-5p and upregulating REV3L	[75, 76, 125]
H19	lncRNA	↑	The H19/miRNA-675 axis is important in the proliferation and EMT transition of cSCC cells	[78]
PRECSIT	lncRNA	↑	PRECSIT promotes cSCC progression by modulating STAT3 signaling	[79]
EZR-AS1	lncRNA	↑	EZR-AS1 increases cSCC cell proliferation, migration and invasion through the PI3K/AKT signaling pathway	[82]
MALAT1	lncRNA	↑	The c-MYC-assisted MALAT1-KTN1-EGFR axis promotes the cSCC progression	[84]
HOTAIR	lncRNA	↑	HOTAIR induces EMT process by regulating EMT-related markers Twist, Snail1 and ZEB1 in cSCC	[114]
CircPVT1	circRNA	↑	The oncogenic circPVT1 promotes cSCC cell migration and invasion	[100]
Circ_0070934	circRNA	↑	Several miRNAs, such as miRNA-1236-3p, miRNA-1238 and miRNA-1247-5p are sponged by circ_0070934, resulting in cSCC cell growth and invasion	[101, 102]
Circ-CYP24A1	circRNA	↑	Exosomal circ-CYP24A1 increases cSCC cell proliferation, migration and invasion, while inducing apoptosis	[132]

number of lncRNAs have crucial cell functions [69]. Furthermore, the aberrant expression of lncRNAs has been linked to a variety of human diseases, including cancer [70]. LncRNAs play a variety of regulatory roles in humans and animals. A great number of lncRNAs appear to act as gene regulators, affecting gene expression both peri- and post-transcriptionally [69]. Considering the crucial roles of lncRNAs in various biological processes, it is foreseeable that their deregulation can lead to human diseases, including human skin cancers.

The regulatory functions of long non-coding RNAs in skin cancers tumorigenicity

LncRNAs have been shown to control cell proliferation, apoptosis, angiogenesis, invasion, and stemness in skin cancers (**Table 2**). Recent research suggests that lncRNAs may potentially play a role in skin tumor microenvironment modification and metastasis [71, 72].

There are not many findings on the role of lncRNAs in the pathogenesis of BCC. More research is needed to properly comprehend the functional importance of lncRNAs in BCC initiation and progression. H19, CASC15, and SPRY4-IT are some of the lncRNAs that are upregulated in BCC [73]. However, the functional analysis of the mentioned lncRNAs in BCC should be subject to further analysis.

Several studies indicated the potential role of the lncRNA PICSAR in cSCC tumorigenicity [74-76]. In cSCC cells and tissues, PICSAR has a high expression level and can serve as a potential biomarker [75]. Moreover, knockdown of PICSAR inhibited cell proliferation and invasion while promoting apoptosis in cSCC cells via the miRNA-125b/YAP1 axis, opening up new possibilities for cSCC therapy [75]. Another study found mechanistic evidence for PICSAR's function in promoting cSCC development by activating the ERK1/2 pathway and downregulating DUSP6 expression [76]. H19 is another well-known lncRNA that is deregulated in different human cancers [77]. H19/miRNA-675 axis promotes development, metastasis, and progression of cSCC [78]. LINC00346, also known as

PRECSIT, is another lncRNA that is highly expressed in cSCC cells [79]. PRECSIT increases invasion of cSCC cells through activating STAT3 and downregulating the expression levels of MMP1, MMP3, MMP10, and MMP13 [79]. EZR-AS1 is a 362 kb lncRNA found on chromosome 6q25.3 [80]. EZR-AS1 expression has been shown to enhance cell motility and mediate cancer cell differentiation [81]. EZR-AS1 knockdown reduced cSCC cell proliferation, migration, and invasion while promoting apoptosis, possibly by modulating the PI3K/AKT signaling pathway [82]. MALAT1 is a famous lncRNA that is considered a critical regulator of tumor development by numerous studies [83]. MALAT1 is activated by UVB irradiation and is significantly expressed in cSCC cells and tumors, according to a new finding [84]. The upregulation of MALAT1 increases cSCC cell proliferation, migration, and invasiveness while suppressing apoptosis [84]. Mechanistically, MALAT1 exerts its oncogenic roles via interacting with c-MYC to form a complex and binding to the promoter region of the KTN1 gene. Indeed, KTN1 acts as the mediator of MALAT1 function in positively regulating EGFR protein expression [84].

The potential roles of lncRNAs in melanoma are well studied [71]. XIST is a lncRNA located on the X chromosome and acts as a major player in the X-inactivation process [85]. In melanoma cells, XIST is highly expressed and contributes to the pathogenicity of disease by sponging miRNA-23a-3p and indirectly targeting GINS2 [86]. Another recent study demonstrated that XIST promotes melanoma metastasis via sponging miRNA-217 [87]. The Cancer Genome Atlas data analysis indicated that FUT8-AS1 expression may associates with the prognosis of melanoma [88]. Further investigations revealed that FUT8-AS1 is downregulated in melanomas in comparison with benign nevi, resulting in poorer overall survival [88]. FUT8-AS1 functions as a tumor suppressor and decreases proliferation, migration, and invasion in melanoma cells [88]. FUT8-AS1 induces miRNA-145-5p biogenesis via binding to NF90, resulting in downregulation of NRAS. As a result, MAPK signaling is suppressed due to NRAS downregulation [88]. The upregulation of lncRNA ZFPM2-AS1 has been identified in melanoma cells [89]. ZFPM2-AS1 promotes melanoma cell proliferation and migration via sponging miRNA-650 and activating NOTCH1 [89]. Another study shows the competing endogenous function of lncRNAs for miRNAs in melanoma [90]. This evidence demonstrated that lncRNA LINC01291 enhances aggressive melanoma features by sponging miRNA-625-5p and thus enhancing the expression of IGF-1R [90]. ATF4 is an integrated stress response controller triggered through nutrient starvation and eIF2 inhibition in melanoma cells [91]. In nutrient-rich conditions, lncRNA TINCR inhibits melanoma invasive phenotypes via suppressing ATF4 translation [92].

The use of immunotherapy in melanoma treatment is continually evolving; ideally, current efforts will result in significant improvements in patient survival. A recent study reported a signature of 15 lncRNAs for predicting survival benefit in melanoma patients treated with anti-PD-1 monotherapy [93]. LncRNAs NARF-AS1, LINC01126, AL442128.2, AC010904.2, AC01-2360.1, AC024933.1, AC022211.4, AC02-2211.2, AC127496.5, AP005329.2, AP0009-19.3, AC023983.1, AC023983.2, AC012615.4 and AC139100.1 are differentially expressed lncRNAs in the training and validation cohorts were associated with the immunological process and therapy [93].

Accumulating evidence suggests the vital role of lncRNAs in skin cancers tumorigenicity. Considering the capacity of lncRNAs in regulating gene expression at various levels, it can be beneficial to evaluate their potential clinical application for skin cancers diagnosis, prognostication, and treatment.

Circular RNAs

Circular RNAs (circRNAs) have received much interest due to their involvement in a wide range of cellular functions that may have a significant impact on phenotype and disease [94]. CircRNAs can influence cellular physiology in a variety of ways, including acting as a decoy for miRNAs or RBPs to alter gene expression or regulatory protein translation. Furthermore, recent findings revealed their biomarker potential in human cancers [94].

CircRNAs are produced through back-splicing, a type of alternative splicing in which the 3' end of an exon binds to the 5' end of its own or an upstream exon via a 3',5'-phosphodiester link, generating a closed structure with a back-splic-

ing junction site [95]. CircRNAs are more stable than linear RNAs because of their covalent closed-loop structure, which protects them from RNase degradation [94]. CircRNAs were formerly defined as noncoding RNAs with regulatory potential [96]. However, it has been proven that they can be translatable RNA molecules [97]. There is a broad definition of multiple mechanisms which illustrate how circRNAs function. They are acting as miRNAs sponges, binding to proteins, translating proteins, and regulating gene expression at various levels [94].

Circular RNAs act as epigenetic regulators in skin cancers

It has been shown that circRNAs play important roles in skin cancers carcinogenesis (**Table 3**). A microarray circRNA expression profiles study introduced 48 downregulated and 23 upregulated circRNAs in BCC [98]. Another study showed that Circ_0005795 expression is considerably higher in BCC tissues and cells and could be served as a promising biomarker for BCC diagnosis [99]. Besides, Circ_0005795 acts as a competing endogenous for miRNA-1231 and promotes BCC cell proliferation [99].

A recent high-throughput sequencing study showed that 449 circRNAs are differently expressed between cSCC and normal adjacent tissue samples [100]. CircPVT1 is one of the upregulated circRNAs in cSCC and knockdown of it prohibits cell migration and invasion [100]. Circ_0070934 is an upregulated circRNA in cSCC that exerts its oncogenic functions via sponging miRNA-1238 and miRNA-1247-5p [101]. HOXB7 is part of a cluster of homeobox B genes located on 17q21.32 [102]. HOXB7 is upregulated in several cancers and contributes to cell proliferation and differentiation [102]. In cSCC cell lines, through competitive binding with miRNA-1236-3p, circ-0070934 regulates HOXB7 expression [102]. Moreover, circ-0070934 knockdown decreased cSCC cell invasive and proliferative potential and induced apoptosis both in vivo and in vitro [102].

Several studies indicated the role of the CXCL chemokine family in human skin cancers, including melanoma [103, 104]. Circ_0020710 upregulates the expression level of CXCL12 through targeting miRNA-370-3p, which leads to melanoma cell proliferation, migration, and invasion [105]. Ccnb1 and Cdk1 are two proteins that form a complex that is involved in the pathogenicity of various cancer types [106]. The circular RNA circ-Ccnb1 interacts with Ccnb1 and Cdk1 proteins and dissociates Ccnb1/Cdk1 complex [106]. By creating a complex with circ-Ccnb1, Ccnb1, and Cdk1, Ccnb1 loses its functions in increasing melanoma cell migration, proliferation, and survival [106]. The circular RNA circ_0001591 is upregulated in the serum of melanoma patients [107]. Circ_0001591 upregulation increased melanoma cell proliferation and invasion while decreasing apoptosis [107]. Mechanistically, high expression of circ_0001591 enhanced PI3K and p-Akt protein production in melanoma through ROCK1 activation via miRNA-431-5p repression [107]. Melanoma cells get the majority of their energy through glycolysis, which is the process by which glucose is converted to lactate for energy, followed by lactate fermentation [108]. Circ_0025039, a circRNA made up of FOXM1 exons, increases glucose metabolism in melanoma via sponging miRNA-198 and upregulating CDK4 [109]. Circ_0002770 is a novel circRNA generated by the well-known oncogene MDM2 [110]. In melanoma cells, circ_0002770 promotes cell proliferation and invasion by sponging miRNA-331-3p [110].

Increasing evidence has revealed that circRNAs play a crucial role in skin cancers progression. These RNA molecules with their closed-loop structure are more stable than other types of noncoding RNAs that influence multiple biological and carcinogenic cascades. CircRNAs are thought to be good biomarkers for liquid biopsies because of their characteristics like stability, specificity, and abundance.

Noncoding RNAs regulation of epithelial-mesenchymal transition in skin cancers

The epithelial-mesenchymal transition (EMT), a vital stage in cancer metastasis, is a dynamic process in which epithelial cells take on mesenchymal characteristics [111]. Although EMT is important during embryonic development and tissue regeneration, it is also implicated in a number of pathologic processes such as tumor initiation and progression, as well as resistance to cancer therapy [112]. EMT is regulated by a variety of EMT-activating transcription factors, and noncoding RNAs have arisen as potential

Table 3. Noncoding RNAs as epigenetic regulators in melanoma

Name	ncRNA class	Expression	Function of ncRNA	Ref.
miRNA-29	miRNA	↧	MAPK/miRNA-29 Axis inhibits melanoma progression by targeting MAFG and MYBL2	[53]
miRNA-633	miRNA	↥	The oncogenic miRNA-633 increases melanoma cell proliferation and migration via targeting KAI1	[54]
miRNA-18a	miRNA	↥	MiRNA-18a-5p suppresses EPHA7 signaling, leads to melanoma cell proliferation and inhibiting apoptosis	[56]
miRNA-27b	miRNA	↧	The miRNA-27b/MYC axis may influence malignant melanoma cell growth	[58]
miRNA-222	miRNA	↥	MiRNA-222 modulates melanoma cell plasticity	[61]
miRNA-1246	miRNA	↥	By suppressing FOXA2, miRNA-1246 promotes melanoma tumorigenicity	[63]
miRNA-92a	miRNA	↥	Expression of miRNA-92a associates with tumor stage and poor prognosis	[64]
miRNA-129-5p	miRNA	↧	CSDE1 exerts it oncogenic functions by inhibiting miRNA-129-5p- in melanoma	[68]
miRNA-214	miRNA	↥	The oncogenic miRNA-214 induces EMT in melanoma by targeting CADM1	[116]
miRNA-200a	miRNA	↧	Tumor suppressor miRNA-200a inhibits melanoma cell proliferation, and migration through modulating the PI3K/Akt signaling pathway and EMT	[117]
miRNA-3662	miRNA	↧	Ectopic expression of miRNA-3662 inhibits EMT process and melanoma cell proliferation by targeting ZEB1	[118]
miRNA-495-3p	miRNA	↧	HDAC3 promotes TRAF5 expression and EMT process through binding to the promoter of miRNA-495-3p	[119]
miRNA-126-3p	miRNA	↧	Downregulation of miRNA-126-3p contributes to dabrafenib resistance via modulating ADAM9 and VEGF-A	[126]
MiRNA-204 and miRNA-211	miRNA	↥	MiRNA-204 and miRNA-211 promote vemurafenib resistance in melanoma by reducing NUAK1/ARK5 protein expression levels	[127]
miRNA-494	miRNA	↥	Melanoma growth and metastasis are prohibited by blocking transported exosome-shuttled miRNA-494	[134]
XIST	lncRNA	↥	XIST contributes to the pathogenicity of melanoma by sponging miRNA-23a-3p and miRNA-217	[86, 87]
FUT8-AS1	lncRNA	↧	FUT8-AS1 downregulation is correlated with poorer overall survival in melanoma patients	[88]
ZFPM2-AS1	lncRNA	↥	ZFPM2-AS1 promotes proliferation and migration in melanoma via sponging miRNA-650 and activating NOTCH1	[89]
LINC01291	lncRNA	↥	LINC01291 promotes aggressive melanoma features by sponging miRNA-625-5p and thus enhancing the expression of IGF-1R	[90]
TINCR	lncRNA	↧	TINCR inhibits melanoma invasive phenotypes in nutrient-rich conditions	[92]
SRA	lncRNA	↥	SRA facilitates EMT process, as well as increasing cell invasion, and proliferation by activating p38 in melanoma cells	[120]
MIAT	lncRNA	↥	MIAT is a regulator of EMT in melanoma by suppressing miRNA-150	[121]
CCAT1	lncRNA	↥	CCAT1 promotes EMT by sponging miRNA-296-3p and upregulating ITGA9 in melanoma	[122]
H19	lncRNA	↥	High expression of H19 causes cisplatin resistance in melanoma cells via suppressing miRNA-18b and increasing IGF1 expression	[128]
TSLNC8	lncRNA	↧	TSLNC8 downregulation lowers the cytotoxic response to BRAF inhibitor PLX4720	[129]
Gm26809	lncRNA	↥	Exosomal lncRNA Gm26809 reprograms normal fibroblasts into CAFs	[137]
Circ_0020710	circRNA	↥	Circ_0020710 regulates CXCL12 by targeting miRNA-370-3p, leads to melanoma cell proliferation, migration and invasion	[105]
Circ-Ccnb1	circRNA	↧	Circ-Ccnb1 decreases melanoma cell migration, proliferation, and survival via dissociating Ccnb1/Cdk1 complex	[106]
Circ_0001591	circRNA	↥	Circ_0001591 upregulation increases melanoma cell proliferation and invasion while decreasing apoptosis	[107]
Circ_0025039	circRNA	↥	Circ_0025039 increases glucose metabolism in melanoma through suppressing miRNA-198 and upregulating CDK4	[109]
Circ_0002770	circRNA	↥	Circ_0002770 promotes melanoma cell proliferation and invasion by sponging miRNA-331-3p	[110]

regulators of these transcription factors' expression and function in various pathologic situations (**Figure 2**) [112].

In cSCC cells, the H19/miRNA-675 axis can affect EMT-related markers, including E-cadherin, vimentin, and N-cadherin, which leads to induc-

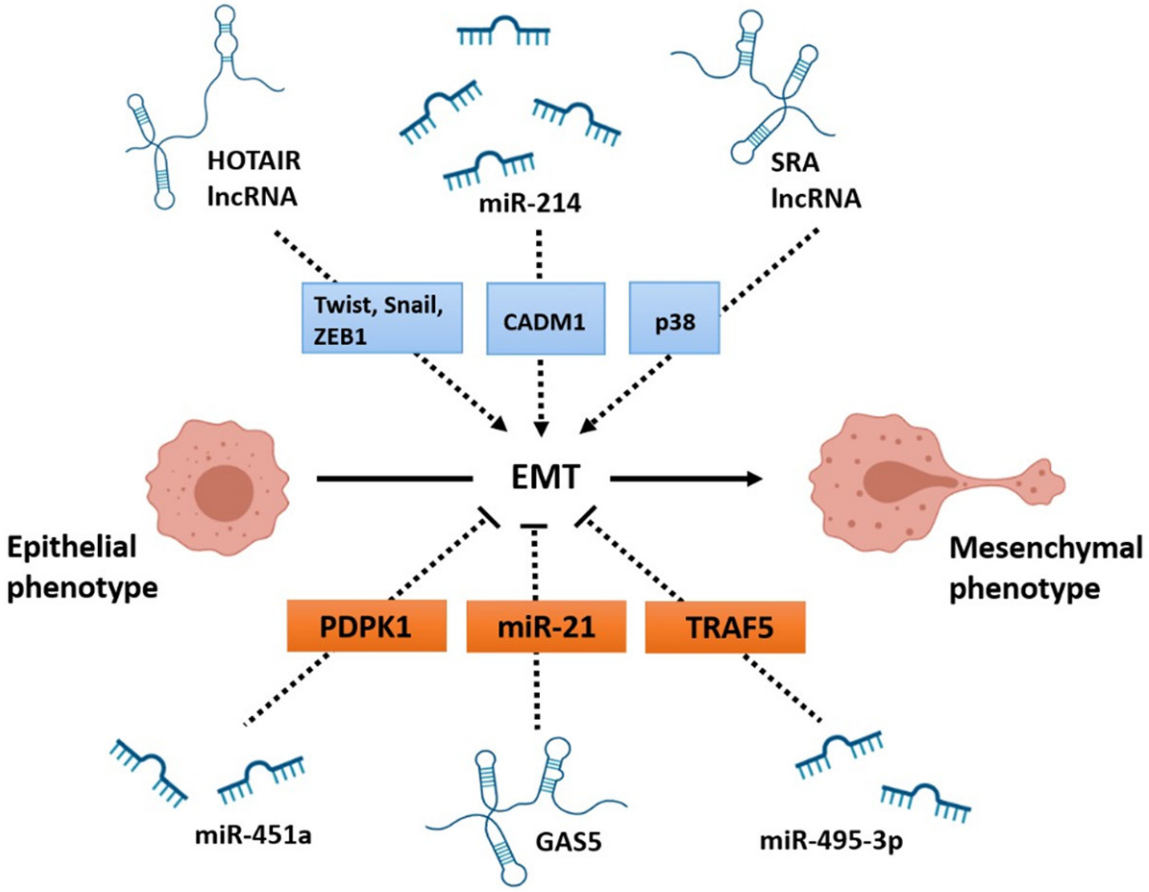

Figure 2. Noncoding RNAs contribute to skin tumor plasticity. Noncoding RNAs that are abnormally expressed may play a key role in EMT processes in skin malignancies by interacting with several signaling cascades.

ing EMT [78]. It has been reported that miRNA-451a is a tumor suppressor and downregulated in cSCC cells [113]. By interacting with PDPK1, ectopic expression of miRNA-451a in cSCC cells inhibited cell proliferation, migration, invasion, and EMT and while inducing cell apoptosis [113]. HOTAIR induces the EMT process by regulating EMT-related markers Twist, Snail1, and ZEB1 in cSCC [114].

CADM1 is a gene that may inhibit the EMT process [115]. A recent study revealed that miRNA-214 induces EMT in melanoma by targeting CADM1 [116]. MiRNA-200a inhibits melanoma cell proliferation, invasion, and migration through modulating the PI3K/Akt signaling pathway and EMT [117]. As mentioned above, ZEB1 is a key regulator of EMT. Ectopic expression of miRNA-3662 inhibits the EMT process and melanoma cell proliferation by targeting ZEB1 [118]. Another study on melanoma showed that miRNA-495-3p expression is decreased, while HDAC3 is upregulated [119]. HDAC3 regulates TRAF5 expression through binding to the promoter of miRNA-495-3p. Furthermore, HDAC3 knockdown upregulates miRNA-495-3p to block the EMT process and oncogenicity of melanoma cells by decreasing TRAF5 [119].

The oncogenic functions of lncRNA SRA are reported in breast and prostate cancers [120]. In melanoma, SRA facilitates the EMT process, as well as increasing cell invasion, and proliferation by activating p38 [120]. The lncRNA MIAT is another regulator of EMT in melanoma that functions as a competing endogenous for miRNA-150-resulted in enhancing the proliferation and invasion [121]. The lncRNA CCAT1 is another example of interaction between lncRNA and miRNA in EMT regulation in melanoma [122]. CCAT1 promotes EMT by sponging miRNA-296-3p and upregulating ITGA9 in melanoma [122].

This evidence proves the significant role of noncoding RNAs in the regulation of the EMT process and may provide novel targets for skin cancer treatment.

Noncoding RNAs in drug-resistant skin cancers

Drug resistance remains the most significant barrier to treating people with skin cancers [123]. Noncoding RNAs participate in inhibiting and promoting cancer drug resistance through various molecular mechanisms. In cSCC, miRNA-3619-5p blocks cisplatin resistance [124]. KPNA4 has been identified as an oncogene that is upregulated in cisplatin-resistant cSCC cells. MiRNA-3619-5p suppresses cSCC cell proliferation and cisplatin resistance by targeting KPNA4 [124]. Several observations indicated the possible role of lncRNAs in cSCC drug resistance. LncRNA PICSAR is highly expressed in cisplatin-resistant cSCC cells [125]. Mechanistically, PICSAR contributes to cisplatin resistance in cSCC cells through targeting miRNA-485-5p and upregulating REV3L [125].

In melanoma cells, miRNA-126-3p is downregulated and contributes to dabrafenib resistance via modulating ADAM9 and VEGF-A [126]. MiRNA-204 and miRNA-211 are two miRNAs that have very similar nucleotide sequences [127]. These miRNAs promote vemurafenib resistance in melanoma by reducing NUAK1/ARK5 protein expression levels [127]. LncRNAs also play a significant role in drug-resistant melanoma. The upregulation of famous lncRNA H19 contributes to cisplatin resistance in melanoma cells via sponging miRNA-18b and increasing IGF1 expression [128]. The lncRNA TSLNC8 is considerably downregulated in BRAF inhibitor-resistant melanoma cells [129]. TSLNC8 downregulation decreases the cytotoxic response to BRAF inhibitor PLX4720 and inhibits apoptosis in PLX4720-treated melanoma cells [129].

Role of exosomal noncoding RNAs in skin cancers

Exosomes are a class of cell-derived extracellular vesicles that are released to the body fluids via multivesicular bodies fusion with the plasma membrane [130]. They have been demonstrated to be carrying cell-specific protein, lipid, and genetic cargoes, such as noncoding RNAs. They can be collected selectively and reprogrammed by surrounding or distant cells far from release [130]. The regulation of exosome formation, particular cargo formations, and cell-targeting specificities are therefore of enormous biological interest, considering the potential of exosomes as noninvasive biomarkers and therapeutic approaches [130]. Recent research has revealed that tumor cells use exosomes to exchange oncogenic noncoding RNAs with one another or with normal surrounding cells [131].

In cSCC cells, exosomal lncRNA PICSAR promotes cisplatin resistance by miRNA-485-5p/REV3L axis [125]. A recent study discovered 25 up-regulated and 76 down-regulated exosomal circRNAs in cSCC patients compared to healthy controls [132]. Exosomal circ-CYP24A1 is upregulated in the serum of cSCC patients [132]. Knockdown of exosomal circ-CYP24A1 restrains cSCC cell proliferation, migration, and invasion while inducing apoptosis [132].

Rab27a and rab27b are two crucial proteins in exosome secretion [133]. In the serum of melanoma patients, exosomal miRNA-494 is increased [134]. However, depletion of Rab27a decreases exosome secretion while increasing the amount of cellular miRNA-494. Following the accumulation of cellular miRNA-494, melanoma cells' malignant behaviors were greatly inhibited by promoting cell apoptosis [134]. These interesting findings suggest that inhibiting transferred exosome-shuttled miRNA-494 could be a promising treatment strategy for melanoma.

Cancer-associated fibroblasts (CAFs) are cells in the tumor microenvironment that enhance tumorigenic characteristics by beginning extracellular matrix remodeling or secreting cytokines [135]. LncRNAs play roles in reprogramming normal fibroblasts into CAFs [136]. Interestingly, melanoma-derived exosomes reprogram normal fibroblasts into CAFs by lncRNA Gm26809 delivery [137].

Concluding remarks and future perspectives

These findings suggest the relevance of noncoding RNAs in skin cancers. MicroRNAs and lncRNAs play an essential role in the pathogenesis of melanoma and non-melanoma carcinomas by regulating cell proliferation, migration,

and invasion at the transcriptional, translational, and post-translational levels. CircRNAs may also be useful as new biomarkers for the early detection of human skin malignancies. Noncoding RNAs play a significant role in the hallmarks of cancer. Their aberrant regulation is correlated with cancer pathophysiological features. They are involved in the first steps of cancer metastasis, including the EMT process. A deeper knowledge of how noncoding RNAs affect EMT progression at various molecular levels can lead to novel anti-metastasis therapy techniques as well as the identification of prognostic or diagnostic markers for skin cancers. Besides, further research into the functions and mechanisms of the identified noncoding RNAs in noncoding RNA-induced cancer cell resistance to chemotherapeutic drugs can provide insight into the treatment of different skin malignancies.

Disclosure of conflict of interest

None.

Abbreviations

PTCH1, Protein patched homolog 1; TERT, Telomerase reverse transcriptase; CDKN2A, Cyclin Dependent Kinase Inhibitor 2A; EGFR, Epidermal growth factor receptor; MAPK, Mitogen-activated protein kinase; ERK, Extracellular-signal-regulated kinase; BRAF, V-raf murine sarcoma viral oncogene homolog B1; TCGA, The Cancer Genome Atlas; DGCR8, DiGeorge Critical Region 8; YAP, Yes-associated protein; FBXW7, F-Box and WD Repeat Domain Containing 7; pi3k, Phosphoinositide 3-kinase; TIMP3, TIMP Metallopeptidase Inhibitor 3; ACVR1, Activin A Receptor Type 1; H3K27ac, Acetylation of histone H3 Lys27; H3K4me3, Trimethylation of histone H3 Lys4; BMP, Bone morphogenetic protein; SMAD1, SMAD Family Member 1; Oct-4, Octamer-binding transcription factor 4; Sirt-1, Silent information regulator 1; Sox2, (Sex determining region Y)-box 2; PTEN, Phosphatase and tensin homolog; MAFG, MAF BZIP Transcription Factor G; KAI1, Kangai 1; EPHA7, EPH Receptor A7; FOXA2, Forkhead Box A2; CSDE1, Cold Shock Domain Containing E1; AGO2, Argonaute RISC Catalytic Component 2; PMEPA1, Prostate Transmembrane Protein, Androgen Induced 1; HOTAIR, HOX antisense intergenic RNA; PRC2, Polycomb repressive complex 2; TERRA, Telomeric-repeat-containing RNA; KCNQ1ot1, KCNQ1 Opposite Strand/Antisense Transcript 1; TUG1, Taurine Up-Regulated 1; CASC15, Cancer Susceptibility 15; MMP1, Matrix metalloproteinase-1; MALAT1, Metastasis Associated Lung Adenocarcinoma Transcript 1; EZR-AS1, EZR Antisense RNA 1; KTN1, Kinectin 1; XIST, X-inactive specific transcript; GINS2, GINS Complex Subunit 2; NRAS, Neuroblastoma RAS viral oncogene homolog; FUT8-AS1, FUT8 Antisense RNA 1; ZFPM2-AS1, ZFPM2 Antisense RNA 1; ATF4, Activating Transcription Factor 4; TINCR, Terminal differentiation-induced non-coding RNA; PD-1, Programmed cell death protein 1; QKI, Quaking; HNRNPL, Heterogeneous nuclear ribonucleoprotein L; HOXB7, Homeobox B7; Ccnb1, Cyclin B1; Cdk1, Cyclin-dependent kinase 1; PDPK1, 3-Phosphoinositide Dependent Protein Kinase 1; ZEB1, Zinc Finger E-Box Binding Homeobox 1; HDAC3, Histone Deacetylase 3; SRA, Steroid receptor RNA activator; MIAT, Myocardial infarction associated transcript; CCAT1, Colon Cancer Associated Transcript 1; ITGA9, Integrin Subunit Alpha 9; KPNA4, Karyopherin Subunit Alpha 4; REV3L, Reversionless 3-like; ADAM9, ADAM Metallopeptidase Domain 9; VEGF, Vascular endothelial growth factor; NUAK1, NUAK Family Kinase 1; IGF1, Insulin-like growth factor 1.

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