Genes & Diseases (2023) 10, 113–125

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REVIEW ARTICLE

Pathogenic roles of long noncoding RNAs in melanoma: Implications in diagnosis and therapies

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Received 14 January 2021; received in revised form 30 July 2021; accepted 20 August 2021
Available online 17 September 2021

KEYWORDS
Cellular functions;
Long noncoding RNAs;
Melanoma

Abstract Melanoma is one of the most dangerous types of cutaneous neoplasms, which are pigment-producing cells of neuroectodermal origin found all over the body. A great deal of research is focused on the mechanisms of melanoma to promote better diagnostic and treatment options for melanoma in its advanced stages. The progression of melanoma involves alteration in different levels of gene expression. With the successful implementation of next-generation sequencing technology, an increasing number of long noncoding RNAs (lncRNAs) sequences have been discovered, and a significant number of them have phenotypic effects in both *in vitro* and *in vivo* studies, implying that they play an important role in the occurrence and progression of human cancers, particularly melanoma. A number of evidence indicated that lncRNAs are important regulators in tumor cell proliferation, invasion, apoptosis, immune escape, energy metabolism, drug resistance, epigenetic regulation. To better understand the role of lncRNAs in melanoma tumorigenesis, we categorize melanoma-associated lncRNAs according to their cellular functions and associations with gene expression and signaling pathways in this review. Based on the mechanisms of lncRNA, we discuss the possibility of lncRNA-target treatments, and the application of liquid biopsies to detect lncRNAs in melanoma diagnosis and prognosis.

Introduction

Melanoma is one of the most aggressive human cancers, accounting for the majority of skin-related cancer deaths worldwide.[1,2] Data from The Lancet showed that there are about 232,100 (1.7%) cases of all newly diagnosed cancers

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Peer review under responsibility of Chongqing Medical University.
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https://doi.org/10.1016/j.gendis.2021.08.007

are cutaneous melanoma, and about 55,500 deaths (0.7% of all cancer deaths) are due to melanoma.[3,4] The incidence of melanoma in Asia is lower than the Oceanian countries.[5] However, the estimated age-standardized mortality rates of cutaneous melanoma in Asia ranged from 0.1 per 100,000 person-years to 1.5 per 100,000 person-years, which shows an accelerating increasing trend.[4] Melanoma development is a multistep process influenced by environmental, genetic, and epigenetic factors. For the Caucasian populations, ultraviolet exposure is one of the major risk factors in superficial spreading melanoma (SSM) cases. In contrast, most of the clinical type in Asia is acral lentiginous melanoma (ALM) that occurs in the area that is not exposed to sunlight.[5] Therefore, the major malignant transformation into melanoma is due to genetic changes. For instance, the frequently found $BRAF^{V600}$ mutation can activate the mitogen-activated protein kinase (MAPK) pathway that can lead to proliferation and metastasis of melanoma cells.[6,7] Moreover, NRAS Q61 K/R mutation can also be found in 20% of melanoma, leading to the activation of MAPK pathways and the phosphoinositide-3-kinase (PI3K) pathway to regulate cyclin D1 and cell cycle-related protein P27.[8] By understanding these mechanisms, researchers have developed the target treatments including BRAF inhibitor dabrafenib and the MEK inhibitor trametinib which can successfully block signaling pathways in BRAFV600-mutant melanoma. For metastatic melanoma, PD-1-based treatment can increase the 5-year overall survival rates from less than 10% to up to 40—50%,[9,10] but relapse rates are also high.[11] Therefore, a better understanding of the mechanisms of melanoma tumorigenesis is required to facilitate early diagnosis and lead to novel effective melanoma treatment strategies.

Nowadays, increasing evidence demonstrate that lncRNAs can regulate various cancers, including melanoma.[12,13] Compared with coding RNAs, non-coding RNAs were initially considered to be the "transcriptional noises" because more than 90% of transcripts from the human genome are not translated into proteins (Fig. 1). Non-coding RNAs consist of long non-coding RNAs (long ncRNAs, lncRNA), microRNAs (miRNAs), transfer RNA (tRNA), ribosomal RNA (rRNA), small nucleolar RNAs (snoRNA), and small nuclear RNA (snRNA). LncRNAs are a kind of noncoding RNA that has more than 200 nucleotides in length. LncRNAs are grouped into different classes based on their genomic location: intergenic, intronic, bidirectional, enhancer, sense, or antisense (Fig. 2); and they can be classified by their function as being signal, decoy, guide, or scaffold.[14,15] LncRNAs can regulate chromatin organization and transcription in the nucleus and modulate mRNA stability, translation and post-translational modification (PTM) in the cytoplasm,[2] playing a vital role in the regulation of diverse biological processes (Fig. 3).

Melanoma is one of the most dangerous types of skin cancer, with a high degree of malignancy and a poor prognosis.[1] Conventional treatments include surgery, chemotherapy, target therapy and immunotherapy. However, patients with advanced stage of melanoma easily gain drug resistance or lose the chance of surgery. As a result, developing novel agents and therapies is an unmet clinical need. Scientists have discovered that lncRNAs govern the onset and progression of human malignancies, particularly melanoma, since more lncRNA sequences are identified. In the current review, we concluded the role of lncRNAs in tumor cell proliferation, invasion, apoptosis, immune escape, energy metabolism, drug resistance, and epigenetic regulation. Given the insightful comprehension of these backgrounds, we can hope to develop specific lncRNA-targeted drugs and treatments.

LncRNAs in melanoma

LncRNAs in cell proliferation and apoptosis

The cell cycle is a series of highly regulated steps that take place in a cell and controlled by specific cyclins, cyclin-dependent kinases (CDKs) and signaling pathways.[16] Studies have shown that lncRNAs promote tumorigeneses by enhancing cell proliferation or evading cell apoptosis.

It has been reported that some lncRNAs are overexpressed in melanoma to boost cell proliferation. For instance, lncRNAs BANCR, NEAT1 and SNHG5 are upregulated in melanoma tissues which can trigger signaling pathways to stimulate cell proliferation by serving as ceRNAs (competing endogenous RNAs), suggesting that lncRNA sponges target miRNA to inhibit the combination between miRNA and mRNA.[17—19] Specifically, lncRNA SPRY4-IT1 can activate the MAPK (mitogen-activated protein kinase) pathway, which plays a crucial role in the malignant transformation into melanoma.[20] The expression of transcription factors or some cell cycle regulatory proteins is regulated by the continuous activation of proliferation pathways. For example, upregulation of lncRNAs GAS6-AS2, FOXC2-AS1, and LINC-PINT results in the increasing percentage of S phase cells and decreasing percentage of G_0/G_1 phase by influencing the expression p15 or INK4 proteins.[21,22—28] Moreover, lncRNA TUG1 can affect cell apoptosis by activating the oncogene Bcl-2 that are the crucial inhibitor of the intrinsic apoptosis pathways.[29,30] The Rb-E2F pathway can also be activated by lncRNA NEAT1 to reduce cell apoptosis.[18,31]

In addition, lncRNAs can also serve as a tumor suppressor to be down-regulated in melanoma. For example, lncRNAs FENDRR, LINC00459, MEG3, HAND2-AS1, and CASC2 are low expressed in melanoma tissues compared with the adjacent normal tissues.[32—44] Downregulation of lncRNA GAS5 in melanoma tissue promotes G_1/S progression by targeting Bcl-2 to activate Cyclin D1, CDK4, and p27 markers.[29,45]

According to the information reported above, lncRNAs induce cancer via various signaling pathways with a "crosstalk" between them (Fig. 4). This may be the reason why melanoma target therapies which focus on single pathway are easy to gain drug resistance. As a result, lncRNA-targeted therapy may serve as a stepping stone for melanoma treatment.[46]

LncRNAs in invasion, migration and metastasis

Epithelial-mesenchymal transition (EMT) is a major process that allows tumor cells to gain the motility in which

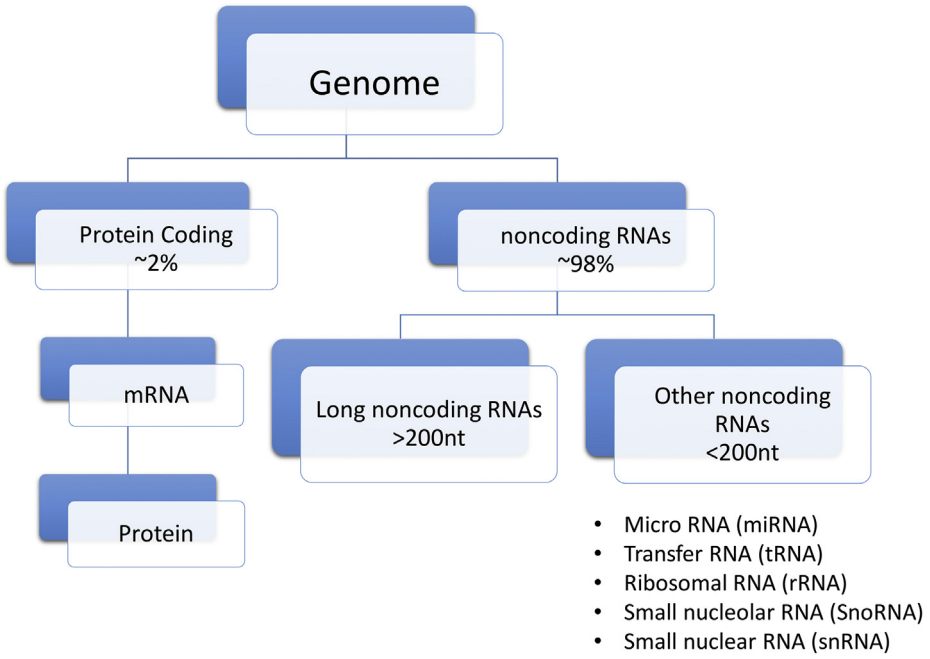

Figure 1 Classification of Genome. More than 90% of transcripts from the human genome are not translated into proteins.

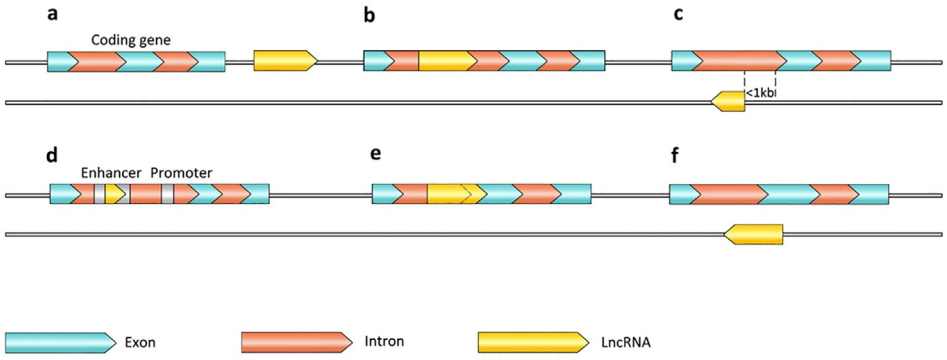

Figure 2 Classification of lncRNAs according to genomic location. **a** Intergenic lncRNAs (lincRNAs) : located between two protein-coding genes. **b** Intronic lncRNAs : located in an intron regions of a coding gene. **c** Bidirectional lncRNAs : located within 1 kb of promoters in the opposite direction from the protein-coding transcripts. **d** Enhancer lncRNAs (elncRNAs) : located in enhancer regions. **e** Sense lncRNAs : transcribed from the sense strand of protein-coding genes and overlap one or several introns and exons. **f** Antisense lncRNAs : transcribed from the antisense strand of protein-coding genes and overlap one or several introns and exons of the sense sequence.

epithelial cells lose adherence by getting deprived of polarity and gaining migratory ability.[47] Specifically, previous studies have defined EMT as upregulation of N-cadherin and Vimentin while deregulation of the E-cadherin process. Furthermore, cell adhesion molecules (CAMs) mediate the recognition and binding between cells and the extracellular matrix, which is important for tumor metastasis. Cadherin is a kind of CAM that regulates the expression of E-cadherin and N-cadherin through the Wnt/β-catenin pathway (see Table 1).

In melanoma, lncRNA CASC15 and UCA1 activate the Wnt/β-catenin pathway to promote cell proliferation and EMT.[48–50] Moreover, lncRNAs can also regulate matrix metalloproteinases (MMPs) which can degrade multiple components in the extracellular matrix (ECM) resulting in tumor metastasis.[51] For example, lncRNA MALAT1 was upregulated in melanoma tissues that lead to EMT by sponging miR-22 through MMP14 and Snail.[52–54] In metastatic melanoma, down-regulation of lncRNA FENDRR can improve cell proliferation, migration, and invasion by modulating the production of MMP2 and MMP9 via the JNK/c-Jun pathway.[55]

From the data, we find that lncRNAs activate the signaling pathways that participate in the EMT process. Also, some studies have proved that lncRNAs mediate the formation of distant lymphatic vessels resulting in the distant metastasis of melanoma. This indicates that the expression level of lncRNAs may serve as a "sentinel lymph node" to help surgeons in determining the extent of surgery or predicting the probability of future metastasis.

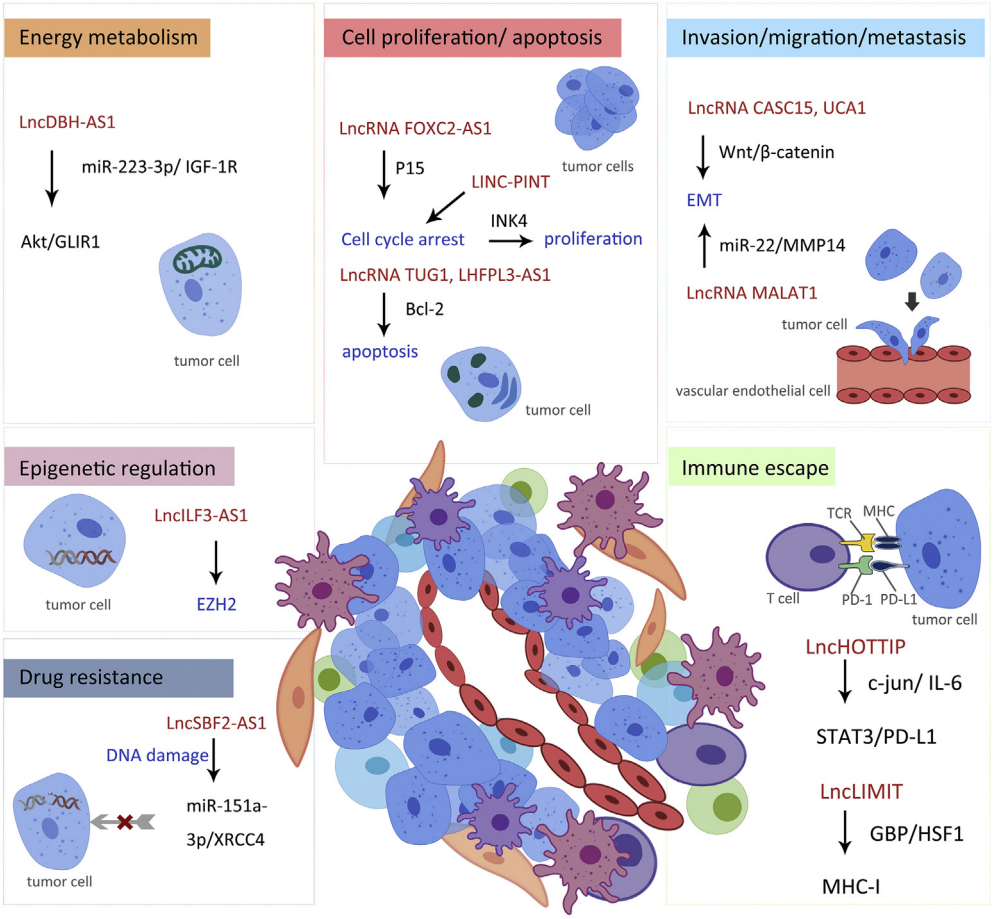

Figure 3 LncRNA regulates tumor cell hallmarks by regulating gene expression and participating in signaling pathway. This figure shows some typical lncRNAs according to their functions in the hallmarks of melanoma.

LncRNAs in the immune system

The immune system plays a critical role in identifying and eliminating cells. However, tumor cells can evade this surveillance through immune escape and immunosuppression[56] by eliminating effector T cells, recruiting regulatory immune cells, and developing an immunosuppressive tumor microenvironment (TME).[57]

LncRNAs have been discovered to have a key regulatory function in cell immune escape.[58,59] Programmed cell death-1 (PD-1) can negatively regulate T cells by binding to its ligand PD-L1 that is highly expressed in tumor cells to mediate immune escape. For instance, lncRNA HOTTIP upregulates the expression of PD-L1 by enhancing the binding of c-Jun and IL-6 to overexpress IL-6 which activates the STAT3/PD-L1 pathway.[60] Moreover, major histocompatibility complex-I (MHC-I) presents tumour antigens to $CD8^+$ T cells and triggers anti-tumor immunity. It was previously reported that lncRNA LIMIT can increase the expression of MHC-I by activating HSF1 through the guanylate-binding protein (GBP) gene.[61] Downregulation of lncRNA FENDRR can sponge miR-423−5p to promote immune escape by activating T-regulatory cells.[32] Moreover, a study from Huang has revealed that lncRNA NKILA interacted with the NF-κB−IκBα complex via directly binding to p65 to increase the sensitivity of antitumor cytotoxic T-lymphocytes (CTLs) and Th1 cells to the activation-induced cell death (AICD) (Fig. 4).[62] Moreover, we have mentioned that overexpression of lncRNA NEAT1 can promote cell proliferation and another study has shown that upregulation of NEAT1 can induce $CD8^+$ T cell apoptosis and target T-cell immunoglobulin and mucin domain 3 (Tim-3) by sponging miR-155.[63] Furthermore, studies showed that lncRNAs can prevent tumor-associated macrophages (TAMs) from polarizing, resulting in the generation of an immunosuppressive tumor microenvironment.[64]

Melanoma is a kind of "hot tumor" which means the tumor microenvironment in melanoma is rich in immune cells. Therefore, melanoma immune treatment strategies are worth exploring. The above studies showed that lncRNAs play a crucial role in immune escape. Also, scientists have proved that delivering small interfering RNA to tumor-associated macrophages can reverse the polarization of macrophages and inhibit the growth of melanoma. We can apply this strategy to boost the lethal impact of tumor cells by targeting the particular lncRNAs found in meditating melanoma immune escape.

LncRNAs in cellular energy metabolism

One of the most basic characteristics of tumor cells is abnormal glucose metabolism. Under both aerobic and

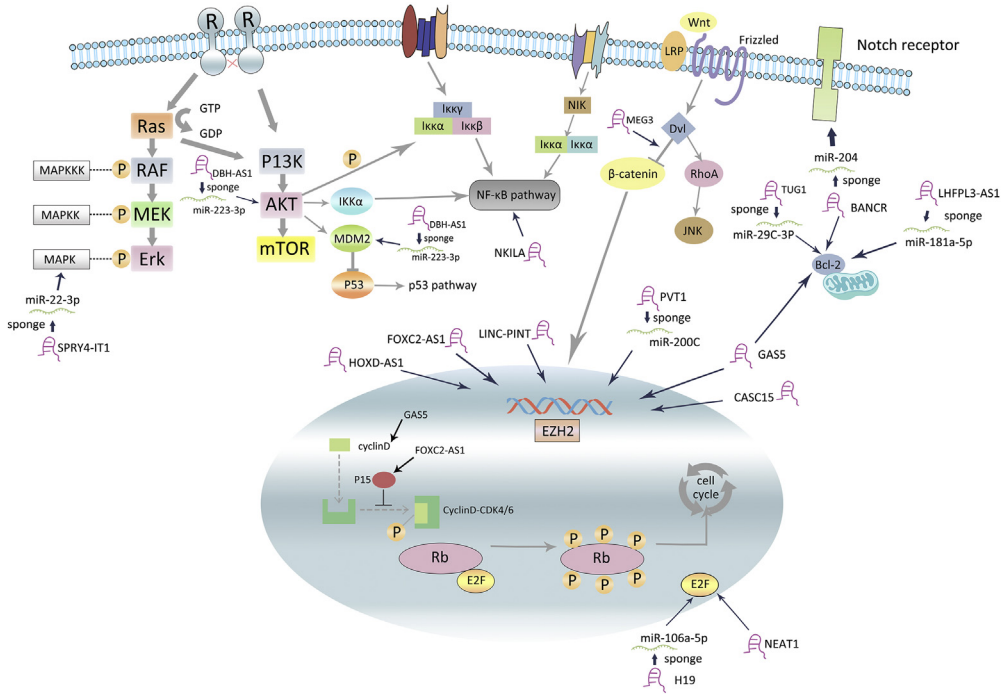

Figure 4 The mechanism of lncRNAs in the development of melanoma. Firstly, lncRNAs can sponge microRNAs to activate some signaling pathways. For instance, the MAPK pathway can be activated by lncRNAs to enhance cell proliferation and the PI-3K-AKT pathway can inhibit cell proliferation by activating the downstream signals. Moreover, the NF-kB pathway meditates immune escape and in melanoma can also be activated by lncRNAs. By activating the Wnt-βcatenin pathway, lncRNAs can participate in the EMT process and promote cell migration and invasion. Secondly, lncRNAs can influence the expression of apoptosis proteins Bcl or alter the cell cycle protein to escape apoptosis. Thirdly, the overexpression of some lncRNAs leads to the epigenetic alterations by affecting the EZH2 gene.

anaerobic conditions, tumor cells demonstrate enhanced glucose to lactate conversion, which is known as the Warburg effect.

For example, lncRNAs CCAT1, H19 and OIP5-AS1 promote glucose metabolism in melanoma.[65–67] In addition, lncRNA DBH-AS1 was reported to regulate glycolytic activity in melanoma through the miR-223–3p/IGF-1R axis that enhances Akt phosphorylation and GLIR1 overexpression to promote tumor cells' glucose intake (Fig. 4). Moreover, lncRNA RNCR2 promotes tumor cell glycolysis and accelerate tumor growth via the miR-495–3p/HK2 axis, and HK2 is important for the aerobic pathway and is a key enzyme for G6P.[68] Moreover, lncRNA GAS5 downregulation was demonstrated to raise the expression of G6PD which in turn raises the ROS level and $NADP^+$/NADPH ratio. This alteration can increase the oxidative stress to influence redox balance in melanoma cells.[69]

However, the latest analysis has brought up to date our understanding of tumor cell glucose metabolism. It was shown that macrophages had the best capability to absorb intratumoral glucose, providing a novel viewpoint on the metabolism relationship between tumor cells and immune cells.[70] As we know, lncRNAs regulate immune cells and tumor cell metabolism. Therefore, the specific role lncRNAs play in this complex process need to be elucidated in the future.

LncRNAs in drug resistance

Early identification and surgical resection are still the best options for treating melanoma, according to clinical studies. For the late stage of melanoma, BRAF inhibitor dabrafenib and immune checkpoint blockade targeting PD-1/PD-L1 have surprising effects in melanoma.[71] However, many patients will eventually develop drug resistance that leads to a poor prognosis. Studies have proved that lncRNAs participated in drug resistance in melanoma.

For example, downregulation of lncTUSC7 was associated with temozolomide (TMZ) resistance by binding miR-10a.[72] LncRNA XIST's overexpression was demonstrated to regulate sensitivity to oxaliplatin by sponging miR-21 to target 3′UTR of PI3KR1.[73] Downregulation of lncRNA TSLNC8 promote the BRAF inhibitor PLX4720 by binding with the catalytic subunit of protein phosphatase 1α (PP1α) to activate MAPK pathway.[74] Previous studies have shown that DNA double-strand break repair can promote TMZ resistance.[75] The upregulation of lncRNA SBF2-AS1 can lead to the development of acquired temozolomide resistance by promoting DNA damage repair through the miR-151a-3p/XRCC4 axis.[76] LncRNA H19 was demonstrated to elevate IGF1 expression in cisplatin-resistant melanoma cells by sponging to miR-18b.[77]

The expression of lncRNAs might be used as a guideline in the treatment of melanoma. Detecting specific lncRNAs

Table 1 The mechanisms of LncRNAs in melanoma tumorigenesis.

LncRNAs	Mode of action	Function	Expression	Target	Phenotypes affected	References
BANCR	Sponge	Oncogene	Up	BANCR/miR-204/Notch2	Cell proliferation↑ Cell viability ↑	17
NEAT1	Sponge	Oncogene	Up	miR-495—3p/E2F3	Cell proliferation↑ Migration ↑ Invasion ↑ Tumor stage ↑	18
				miR-224—5p		121
				miR-200b-3p/SMAD2		122
SNHG5	Sponge	Oncogene	Up	miR-26a-5p/TRPC3	Cell proliferation↑ Apoptosis ↓ Invasion ↑	19
FENDRR	—	Tumor suppressor	Down	miR-423—5p	Cell proliferation↑ Migration ↑ Invasion ↑ T-regulatory cells↓ Immune escape	32
LINC00459	Sponge	Tumor suppressor	Down	miR-218/DKK3	Cell proliferation↑ Migration ↑ Invasion↑ Survival↓	33
LINC00888	Sponge	Oncogene	Up	miR-216/CRK	Cell proliferation↑ Apoptosis↓ EMT↑	123
FOXD3-AS1	Sponge	Oncogene	Up	miR-127—3p/FJX1	Cell proliferation↑ Migration ↑ Invasion ↑ Apoptosis↓	124
HOXA11-AS	Sponge	Oncogene	Up	miR-153—3p/ITGA9	Cell proliferation↑ EMT ↑ Invasion ↑ Apoptosis↓	125
MEG3	Sponge	Tumor suppressor	Down	miR-21/E-cadherin	Cell proliferation↑	36
				wnt	EMT↑ GO/G1↓ Tumor growth↑	34
				miR-499—5p/CYLD	Tumor metastasis↑ Invasion ↑ Migration ↑	35
HAND2-AS1	—	Tumor suppressor	Down	ROCK1↑	Cell proliferation↑ Tumor stage↑	37
SSATX	—	Oncogene	Up	Wnt/β-Catenin	Cell proliferation↑ Migration ↑ Invasion ↑	126
LINC00518	Decoy	Oncogene	Up	miR-204—5p/AP1S2	Migration ↑ Invasion ↑	127
LINC00665	Sponge	Oncogene	Up	miR-224—5p/VMA21	Cell proliferation↑ Migration ↑	128
CASC2	Sponge	Tumor suppressor	Down	miR-18a-5p/RUNX1	Cell proliferation↓	38
				miR-181a/PLXNC1	Migration ↑ Invasion ↓	129
CASC15	—	Oncogene	Up	PDCD4/EZH2	Cell proliferation↑	82
				Wnt/β-Catenin	Apoptosis ↓ Invasion ↑ EMT↑	48
SPRY4-IT1	Sponge	Oncogene	Up	miR-22—3p/MAPK	Cell proliferation↑ Migration ↑ Invasion ↑ EMT↑	20
SLNCR1	Guide	Oncogene	Up	AR/Brn-a/MMP9	Invasion ↑ OS↓	130
UCA1	Sponge	Oncogene	Up	miR-185—5p/Wnt/β-Catenin	Invasion ↑ EMT↑ Tumor growth↑	50
MALAT1	Sponge	Oncogene	Up	miR-22/MMP14/Snail	Cell proliferation↑ Migration ↑ Invasion ↑	54
ATB	Sponge	Oncogene	Up	miR-590—5p/YAP1	Cell proliferation↑ Apoptosis ↓ Invasion ↑ G1↓ S↑ Tumor growth ↑	28
CRNDE	Sponge	Oncogene	Up	miR-205/CCL18	Cell proliferation↑ Migration ↑ Invasion ↑ Apoptosis ↓ G1↓ S↑	131
AFAP1-AS1	Sponge	Oncogene	Up	miR-653—5p/RAI14	Cell proliferation↑ Migration ↑ Invasion ↑ EMT↑	132
OR3A4	—	Oncogene	Up	Wnt/β-catenin	Migration ↑ Invasion ↑	133
GAS6-AS2	—	Oncogene	Up	GAS6/AXL/AET/ERK	Cell proliferation↑ Apoptosis↓	22
FOXC2-AS1	Guide	Oncogene	Up	Recruit EZH2 to inhibit p15 transcription	Cell proliferation↑ Apoptosis ↓	23
LINC-PINT	—	Tumor suppressor	Down	EZH2	Go/G1↑ Migration ↑ Invasion ↑	24
TUG1	Sponge	Oncogene	Up	miR-29c-3p/BCL-2 MMP2/RGS1	Poor prognosis	30
				MiR-129—5p/AEG-1/Bcl-2,MMP9,CyclinD1,Caspase3	Cell proliferation↑ Apoptosis↓ Invasion ↑ G0/G1↓	134
CPS1-IT1	—	Tumor suppressor	Down	BRG/Cyr61	Migration ↑ Invasion ↑ EMT↑ Angiogenesis ↑	135
LHFPL3-AS1	Sponge	Oncogene	Up	miR-181a-5p/Bcl-2	Cell proliferation↑ G0/G1↓ Migration ↑	136

Table 1 (*continued*)

LncRNAs	Mode of action	Function	Expression	Target	Phenotypes affected	References
					Invasion ↑	
LINC00963	Sponge	Oncogene	Up	miR-608/NACC1	Poor prognosis Cell proliferation↑ Migration ↑ Invasion ↑	137
FALEC	Guide	Oncogene	Up	EZH2/p21	Cell proliferation↑ Apoptosis ↓ EMT↑ Invasion↑ Metastasis↑ Poor prognosis G0/G1↓	138
HCP5	Sponge	Tumor suppressor	Down	miR-12/RARRES3	Cell proliferation↑ Invasion↑ Apoptosis ↓ Poor prognosis	100
SRA	—	Oncogene	Up	p38	Cell proliferation↑ Invasion↑ Apoptosis ↓Migration ↑ Metastasis↑ EMT↑	139
RP11-705C15.3	Sponge	Oncogene	Up	miR-145—5p/NRAS/MAPK	Cell proliferation↑ Invasion↑ Apoptosis ↓Migration ↑	140
ZFPM2-AS1	Sponge	Oncogene	Up	miR-650/Notch1	Cell proliferation↑ Apoptosis ↓Migration ↑	141
DIRC3	Signal	Tumor suppressor	Down	SOX10/IGFBP5	Cell proliferation↑ Invasion↑ Metastasis↑	142
NR2F1-AS1	Sponge	Oncogene	Up	miR-493—5p/GOLM1	Cell proliferation↑ Metastasis↑ Poor prognosis	143
GAS5	Sponge	Tumor suppressor	Down	GAS5↓→G6PD↑→ROS↑→Bcl-2↑CyclinD1↑	Tumor stage ↑ G0/G1↓ Oxidative stress↑ Cell viability↑	45
				EZH2/CDKN1C	Migration↑ Invasion↑	69
				MMP2		51
				miR-137		144
HOTTIP	—	Oncogene	Up	C-jun/IL-6/PD-L1	Immune escape T cell proliferation↓ T cell activity↓	60
LIMIT	—	Tumor suppressor	Down	GBP/HSF1/MHC-I	MHC-I expression↓	61
NKILA	—	Tumor suppressor	Down	NF-kB/p65	Immune escape↑	62
					Cell proliferation↑ Migration ↑ Invasion ↑	145
CCAT1	Sponge	Oncogene	Up	miR-296—3p/ITGA9	Glucose metabolism↑ Cell proliferation↑ GO/G1↓ EMT↑	65
LINC01550	—	Tumor suppressor	Down	—	Cell proliferation↑ Invasion ↑ GO/G1↓ Poor prognosis Apoptosis ↓	146
H19	Sponge	Oncogene	Up	miR-18b/IGF1	Sensitivity to cisplatin↓	77
				miR-106a-5p/E2F3	Glucose metabolism↑ OS↓	66
				NF-KB/PI3K/AKT	Cell proliferation↑ Migration ↑ Invasion ↑Poor prognosis	147
OIP5-AS1	Sponge	Oncogene	Up	miR-217/GLS	Glutamine catabolism↑ OS↓	67
RNCR2	Sponge	Oncogene	Up	miR-495—3p/HK2	Glucose metabolism↑ Cell proliferation↑ EMT↑	68
SNHG6	Sponge	Oncogene	Up	miR-101—3p/RAP2B	Cell proliferation↑ Migration ↑ Invasion ↑	148
DBH-AS1	Sponge	Oncogene	Up	miR-223—3p IGF-1R/Akt/GLU1	Glycolytic activity ↑ Cell proliferation↑ Migration ↑ Invasion ↑	149
TUSC7	Sponge	Biomarker	Down	miR-10a	Temozolomide resistance	72
POU3F3	Sponge	Oncogene	Up	miR-650/MGMT	Dacarbazine resistance	150
TSLNC8		Tumor suppressor	Down	PP1α/MAPK	BRAF inhibitor resistance	74
XIST	Sponge	Oncogene	Up	miR-139—5p/ROCK1	Cell proliferation↑Migration ↑ Invasion ↑	42
				miR-21/PI3KR1	Sensitivity to oxaliplatin↓	73
SBF2-AS1	Sponge	Oncogene	Up	miR-151a-3p/XRCC4	DNA damage repair↓ Sensitivity to Temozolomide↓	76

(*continued on next page*)

Table 1 (*continued*)

LncRNAs	Mode of action	Function	Expression	Target	Phenotypes affected	References
LINC01291	Sponge	Oncogene	Up	miR-625—5p/IGF-1R	Cell proliferation↑ Migration ↑ Invasion ↑ Colony formation↑ Sensitivity to cisplatin↓	151
ILF3-AS1	—	Oncogene	Up	ILF3/ILF3-AS1	Poor survival Cell proliferation↑ Migration ↑ Invasion ↑	79
HOXD-AS1	—	Oncogene	Up	RUNX3/EZH2	Cell proliferation↑ Invasion ↑ OS↓	80
PVT1	Sponge	Oncogene	Up	miR-200c/EZH2	Cell proliferation↑ Migration ↑ Invasion ↑ EMT↑ G0/G1↑	83
LNMAT1	—	Oncogene	Up	EZH2/CADM1	Migration ↑ Invasion ↑	152
LINC0638	—	Oncogene	Up	—	Cell proliferation ↑ Local recurrence↑ Tumor stage ↑	92
FOXD2-AS1	—	Oncogene	Up	Akt	Tumor stage ↑ Poor survival Cell proliferation↑ Migration ↑ Invasion ↑	153
MIR31HG	—	Oncogene	Up	—	Poor prognosis Cell proliferation↑ Migration ↑ Invasion ↑	93
LINC00173	Sponge	Oncogene	Up	miR-493/IRS4	Lymph node metastasis↑ OS↓ Cell proliferation↑ Migration ↑ Invasion ↑	94
LINC00520	Sponge	Oncogene	Up	miR-125b-5p/EIF5A2	Cell proliferation↑ Migration ↑ Invasion ↑ Survival↓	96
DSCAM-AS1	Sponge	Oncogene	Up	miR-136	Cell proliferation↑ Migration ↑ Invasion ↑ Survival↓ Colony formation↑	154
LUADT1	Sponge	Oncogene	Up	miR-28—5p/RAP1B	Poor Survival	97
MHENCR	Sponge	Oncogene	Up	miR-425/miR-489 IGF1/SPIIN1 PI3K-AKT	Poor prognosis Cell proliferation↑ Migration ↑	155
TTN-AS1	—	Oncogene	Up	TTN-AS1/TTN	Poor prognosis Cell proliferation↑ Migration ↑	99

is a non-invasive and convenient way to assess the risks of patients to gain drug resistance and help physician to determine which drugs or combination is suitable for patients.[78] Furthermore, by targeting some lncRNAs, we may increase the efficacy of medication in the future.

LncRNAs in epigenetic regulation

Changes in gene expression levels that are not accompanied by changes in the nucleotide sequence of the gene that encodes proteins are referred as epigenetic regulation. It includes DNA methylation, histone modification, and post-transcriptional regulation of non-coding RNA.

The EZH2 gene encodes a histone-lysine N-methyltransferase that can methylate the 27th lysine of histone H3 (H3K27me3) which results in the alteration of epigenetics. The methylation activity of EZH2 promotes the formation of heterochromatin to silence genes' expression.

For instance, lncRNA ILF3-AS1 epigenetically activates ILF3 expression by changing the location of EZH2 and further modulates the repressive chromatin marker histone H3 lysine 27 tri-methylation (H3K27me3) levels to promote melanoma proliferation, migration and invasion.[79] Moreover, lncRNA HOXD-AS1 was disclosed to be overexpressed in melanoma, resulting in cell proliferation and invasion by epigenetically silencing RUNX3, a tumor suppressor in some carcinomas, through EZH2.[80,81] Downregulation of lncRNA GAS5 reduces H3K27 trimethylation and regulates CDKN1C expression to accelerate oxidative stress in melanoma by inhibiting EZH2.[69] In addition, the upregulation of CASC15 modulated cell proliferation and invasion by targeting PDCD4 and EZH2.[82] PDCD4 is a previously reported tumor suppressor that was down-regulated by PRC2 complex through upregulating H3K27me3 at its promoter.[39] LncRNA PVT1 leads cell cycle arrest and EMT in melanoma cells through miR-200c/EZH2 axis (Fig. 4).[83]

To assist in better understanding the mechanism of lncRNA in melanoma carcinogenesis, we constructed a schematic to depict the signaling pathways involved in cell proliferation, invasion, apoptosis, immune evasion, energy metabolism, drug resistance, and epigenetic control.

Conclusions and future perspectives

In the early stages of melanoma, histopathologic examination, the conventional gold standard procedure, is unable

to provide a proper diagnosis.[84] Therefore, there is an urgent and unmet need for a more personalized and precise diagnosis of melanoma. Liquid biopsies provide non-invasive and easy sources of circulating RNAs.[12–14] Different types of both long and shorter non-coding RNAs are detected in the whole blood, serum, and plasma.[15] Therefore, lncRNAs can be developed as new diagnosis and prognosis method of melanoma.[85–90] The abnormal expression of HOTAIR, for instance, has been seen not only in lymphocytes surrounding metastatic tumor cells in melanoma patients, but also in their serum, indicating that it may be used as a biomarker for early diagnosis.[91] Moreover, lncRNA LINC0638 was significantly upregulated in both biopsies and plasma with increasing tumor stage and tumor size compared with adjacent healthy tissue.[92] LncRNA (MIR31HG, GAS5, LINC00173) levels were associated with lymph node metastasis, distal metastasis and TNM stage.[45,93,94] Besides, some lncRNAs (HAND2-AS1, MEG3) are downregulated in melanoma tissue with the increase in tumor stage.[36,37] Moreover, lncRNAs are associated with tumor overall survival and disease-free survival. For example, the upregulation of lncRNAs (FGD5-AS1, HOXD-AS1, GAS6, LINC00520, LUADT1) leads to shorter OS.[27,80,95–97] LncRNA (ILF3-AS1, TTN-AS1) overexpression makes melanoma more likely to metastasize, which leads to poorer prognosis due to its severity.[79,98,99] Moreover, the downregulation of lncRNAs (HCP5, OIP5-AS1) limits the melanoma progression.[67,100] Bringing all evidence together, lncRNAs have potential diagnostic values to instruct treatments and assess the prognosis of melanoma.

As we reviewed the most recent research on lncRNAs in melanoma, we discovered that there are still several limitations to existing research. To begin with, little is known about the involvement of lncRNAs in the tumor microenvironment (TME). A previous study has shown that lncRNA TINCR can alter melanoma cells' phenotypes from proliferative to invasive by preventing the binding between mRNA and ribosomes.[101] The nutrient deprivation or extracellular signals from the tumor microenvironment play an important role in phenotype plasticity in melanoma. Therefore, the relationship between lncRNAs and TME in phenotype plasticity generation in melanoma need to elucidated.[102] By understanding the influence of lncRNA on melanoma cells' phenotypes, we wonder if lncRNAs control the formation of melanoma subtype (cutaneous, mucosal, acral, uveal). Secondly, various research studies have proved that melanoma secreted vesicles carrying mircoRNA[103] or directly secreted cytokines to reform tumor microenvironment[104,105] to promote the blood vessels and lymphatic generation[106] and they can also target T cells, bone marrow suppression cells (MDSC) and NK cells to create an immunosuppression environment.[107–110] Based on current understanding, existing evidences suggest that LncRNAs mediated intercellular communication by secreting vesicles or cytokines.[111,112] Whether the formation of distant lymphatic vessels which leads to tumor metastasis is due to exosomes that carry lncRNAs needs to be explained in the future. Thirdly, the research using nanomaterials to carry siRNA to inhibit melanoma growth shows great success. How to transfer this method into clinical melanoma treatment is an interesting topic. Finally, the understanding of the causes of lncRNAs in upstream signaling pathways is not enough to tell us when and why DNA starts transcribing lncRNAs. Therefore, the knowledge of lncRNAs is still limited, and needs more development.

Melanoma overall fatality rates are determined by tumor stages and therapy.[4] As scientists have understood the mechanisms of melanoma better, surgery is not the only way to treat it. Target treatments and immune therapies have translated melanoma treatments into a new era.[113,114] Treatments that target B-Raf proto-oncogene serine/threonine-kinase (BRAF)V600 (Val600) mutations using selected BRAF inhibitors combined with mitogen-activated protein kinase inhibitors have significantly improved prognosis.[4,115,116] The clinical practice of PD-1 antibodies and cytotoxic T lymphocyte-related antigen 4 (CTLA-4) antibodies as cancer immunotherapy have also resulted in a decrease in mortality. However, these options above for patients with metastatic melanoma are not effective.[113,114,117–120] According to the facts presented above, developing a novel melanoma therapy strategy is crucial. LncRNA-target method in melanoma treatment has a promising perspective. Antisense oligonucleotides (ASOs), which may form a DNA-RNA structure with target RNA, can trigger RNA degradation. This method is a potential way to target those lncRNAs that are overexpressed in melanoma. Recent studies have found that CRISPR/Cas9 can silence the transcription of the lncRNAs to treat cancers. The virus is a superior RNA interference. Many reports have shown the huge potential of shRNA to target lncRNAs in cancer treatments.

Their translation into clinical practice will necessitate further research and clinical trials in the future. LncRNAs may help us better understand ourselves and treat this devastating disease in the future by redrawing the blueprint of genes.

Conflict of interests

The authors have declared that no competing interest exists.

Funding

This work was supported by the National Natural Science Foundation of China (No. 81871578).

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