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REVIEW ARTICLE

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Long non-coding RNAs in melanoma

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Abstract

Melanoma is the most lethal cutaneous cancer with a highly aggressive and metastatic phenotype. While recent genetic and epigenetic studies have shed new insights into the mechanism of melanoma development, the involvement of regulatory non-coding RNAs remain unclear. Long non-coding RNAs (lncRNAs) are a group of endogenous non-protein-coding RNAs with the capacity to regulate gene expression at multiple levels. Recent evidences have shown that lncRNAs can regulate many cellular processes, such as cell proliferation, differentiation, migration and invasion. In the melanoma, deregulation of a number of lncRNAs, such as HOTAIR, MALAT1, BANCR, ANRIL, SPRY-IT1 and SAMMSON, have been reported. Our review summarizes the functional role of lncRNAs in melanoma and their potential clinical application for diagnosis, prognostication and treatment.

1 | INTRODUCTION

Melanoma is the leading cause of skin cancer-related deaths and characterized by high metastatic potentials.[1-3] The incidence of melanoma has been increasing in recent years, and is generally higher in fair-skinned population.[4,5] For early-stage melanoma, surgery remains the mainstay of treatment with a high cure rate.[6] However, prognosis of advanced melanoma is dismal because of its resistance to conventional therapies, including chemotherapy and radiotherapy.[7] Early melanoma detection is therefore the key to improving the survival. Nevertheless, the histopathologic diagnosis of melanoma is sometimes difficult for dermatopathologists in a subset of cases.[8] Moreover, there is no sensitive and specific biomarker for melanoma owing to its unclear molecular pathogenesis.

It has been demonstrated that more than 90% of transcripts from the human genome are not translated into proteins.[9] These non-protein coding RNAs are an important class of regulatory molecules that play crucial roles in the regulation of gene expression [10] and their dysregulation has been implicated in the development of different types of cancer.[11,12] Non-coding regulatory RNAs are classified into two categories depending on their length: small non-coding RNA (≤200 bp) and long non-coding RNA (lncRNA, >200 bp).[13,14] LncRNA can modulate gene expression through various mechanisms, including chromatin modification, transcriptional activation/repression, RNA editing/splicing/degradation, microRNA sequestration, and translational efficiency regulation.[15,16] Historically, lncRNAs were dismissed as junk or nonfunctional transcriptional noise.[17] However, emerging evidence has demonstrated that lncRNAs play crucial functional roles in tumourigenesis, including melanoma.[18]

In this review, we summarize the published data on the deregulation and functions of lncRNAs in melanoma. We also discuss their potential diagnostic, prognostic and therapeutic applications.

2 | DEREGULATED LNCRNAS IN MELANOMA

2.1 | Hotair

The HOX transcript antisense intergenic RNA (HOTAIR), which was named for its location at the antisense strand of the HOXC gene cluster, was initially identified to be an overexpressed lncRNA in primary and metastatic breast cancer.[19] By recruiting polycomb repressive complex 2 and histone demethylase complex, HOTAIR was found to mediate gene silencing via tri-methylation of lysine 27 on histone H3 (H3K27me3) and H3K4me2.[19] Numerous studies have shown that HOTAIR expression is upregulated in human

cancers, including breast, gastric, hepatocellular, colorectal, pancreatic and nasopharyngeal carcinomas,[14,20-24] in which overexpression of HOTAIR plays an oncogenic role and is associated with cancer metastasis and poor prognosis. In melanoma, HOTAIR was consistently overexpressed in lymph-node metastasis as compared with primary lesions.[25] In addition, knockdown of HOTAIR suppressed the motility and invasion of melanoma cells in vitro, accompanied by decreased ability to degrade gelatin matrix, indicating that HOTAIR might increase melanoma cell invasiveness through promoting gelatinase activity. Another study showed that none of the benign melanocytic lesions showed the presence of HOTAIR whereas the staining of HOTAIR was very weak in primary non-metastatic melanomas but very strong in all pairs of primary tissues and corresponding metastases. Interestingly, HOTAIR could be detected in intratumoural lymphocytes as well as in the serum of a subset of metastatic patients.[26] Portoso et al. showed that HOTAIR RNA can repress transcription in the context, but that this effect is PRC2 independent.[27] Taken together, these data suggested that HOTAIR is involved in the metastatic progression of melanoma and may serve as a diagnostic marker for metastatic melanoma.

2.2 | Malat1

The metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), also known as nuclear-enriched transcript 2 (NEAT2),[28] was initially identified as a prognostic marker for lung cancer metastasis.[9] Accumulating studies have now demonstrated MALAT1 deregulation in different human malignancies.[29] It has been shown that MALAT1 mainly plays an oncogenic role in tumourigenesis through promoting cancer-cell proliferation, migration and invasion.[30,31] MALAT1 expression levels were higher in melanoma as compared with adjacent normal tissues.[32] Moreover, knockdown of MALAT1 decreased the migration of melanoma cell line in vitro. A recent study also demonstrated that knockdown of MALAT1 promoted miR-140 expression and suppressed Slug and ADAM10 expression in the uveal melanoma cell line MUM-2C.[33] These findings suggest that the aberrant upregulation of MALAT1 might contribute to melanoma metastasis through promoting cell migration via derepressing miR-140-mediated inhibition of Slug and ADAM10.

2.3 | Bancr

BRAF-activated non-coding RNA (BANCR) is a 4-exon transcript of 693 bp, whose encoding gene is located on chromosome 9.[34,35] BANCR is involved in a variety of human malignancies, including lung carcinoma, colorectal cancer, melanoma, gastric cancer and bladder cancer.[36-40] Nevertheless, the direction of deregulation of BANCR was tissue-specific in which this lncRNA could act as an oncogene or tumour-suppressor gene.[41] In melanoma, Flockhart and colleagues demonstrated that BANCR was recurrently overexpressed.[35] Moreover, knockdown of BANCR decreased melanoma cell migration and this effect could be rescued by the chemokine CXCL11. Another study also showed that BANCR expression was upregulated in melanoma cell lines and tissues.[42] In addition, its expression level was increased with advancing melanoma stages. Knockdown of BANCR expression significantly reduced the proliferation of melanoma cells through inactivating the extracellular signal–regulated kinases 1/2 (ERK1/2) and c-Jun N-terminal kinase (JNK) components of the mitogen-activated protein kinase (MAPK) pathway. Moreover, BANCR knockdown suppressed melanoma growth in nude mice. Pertinent to clinical practice, patients with high BANCR expression in melanoma tissues showed a poorer prognosis and lower survival rate. These data indicated overexpression of BANCR contributes to the promotion and progression of melanoma.

2.4 | Spry4-it1

SPRY4-IT1 is derived from an intron of the *SPRY4* gene localized in the chromosomal region 5q31.3, which encodes an endogenous inhibitor of the receptor-transduced mitogen-activated protein kinase pathway.[43] The secondary structure of SPRY4-IT1 contains several long hair-pins. It was initially identified to be upregulated in melanoma.[43] In recent years, emerging studies have demonstrated the deregulation and pathogenic roles of SPRY4-IT1 in human cancers, including lung cancer, gastric cancer, breast cancer and colorectal cancer.[44-47] In melanoma, SPRY4-IT1 expression was predominantly localized in the cytoplasm.[48] Knockdown of SPRY4-IT1 impeded cell proliferation and differentiation but promoted apoptosis in melanoma cells.[43] Differential expression of both SPRY4 and SPRY4-IT1 was also detected in patient samples of primary in situ, regional metastatic, distant metastatic, and nodal metastatic melanoma. A subsequent mechanistic study identified lipin 2 as a major binding partner of SPRY4-IT1. Lipin 2 is an enzyme that converts phosphatidate to diacylglycerol. Moreover, knockdown of SPRY4-IT1 not only increased the protein expression of lipin 2, but also elevated the levels of diacylglycerol O-acyltransferase 2 that converts diacylglycerol to triacylglycerol. Concordantly, SPRY4-IT1 knockdown increased the levels of several lipid species, including fatty acyl chains, acyl carnitine and triacylglycerol.[49] These findings indicated that aberrant upregulation of SPRY4-IT1 plays a significant role in the pathogenesis of melanoma through promoting lipid synthesis.

2.5 | Anril

ANRIL (antisense non-coding RNA in the INK4 locus) is named since it is expressed in the opposite direction from the INK4A-ARF-INK4B gene cluster.[50] *ANRIL* gene has been reported to be a genetic susceptibility locus shared by coronary heart disease, type 2 diabetes and also cancers.[51] ANRIL was significantly upregulated in many cancers, including gastric cancer, non-small cell lung carcinoma, ovarian cancer and gallbladder cancer.[52-55] Chromosome 9p21, which harbours *ANRIL* gene, is frequently inactivated in multiple human cancers.[56] Moreover, recurrent fusion transcripts of *MTAP* and *ANRIL* can be detected in ~25% of melanoma cell lines and tumour tissues.[6] In another study, ANRIL was shown to be upregulated whereas INK4A and INK4B were downregulated in uveal and cutaneous melanoma

tissues and melanoma cell lines. Interestingly, knockdown of ANRIL restored INK4A and INK4B expression and inhibited colony formation and migration in vitro and growth of melanoma xenograft in vivo.[57] These findings indicate that ANRIL exerts its oncogenic action in melanoma probably through regulation of its encoding locus that also harbours the tumour suppressors INK4A and INK4B.

2.6 | Llme23

Wu and colleagues identified a previously unreported lncRNA known as Llme23 in a human melanoma cell line. This lncRNA was found to interact with polypyrimidine tract-binding protein-associated splicing factor (PSF). In addition, Llme23 expression was exclusively detected in human melanoma lines.[58] Knockdown of Llme23 remarkably inhibited the malignant phenotypes of melanoma cells and deceased expression of the proto-oncogene Rab23. These findings suggest that Llme23 might play an oncogenic role in human melanoma through direct binding to PSF.

2.7 | Uca1

Urothelial carcinoma associated 1 (UCA1) was initially identified to be upregulated in bladder cancer cells.[59] UCA1 expression was significantly upregulated in melanomas compared with paired adjacent normal tissues.[32] Moreover, the expression level of UCA1 was significantly higher in more advanced stages (stages 3-4) melanoma than those at early stages (stages 1-2). Knockdown of UCA1 inhibited the migration of melanoma cells. A subsequent mechanistic study demonstrated that UCA1 could sponge miR-507 and derepress miR-507-mediated inhibition of FOXM1 expression in melanoma, leading to increased cell proliferation and invasion.[60] These findings indicate that increased UCA1 expression might contribute to melanoma growth and metastasis through the miR-507-FOXM1 axis.

2.8 | Slncr1

SRA-like non-coding RNA1 (SLNCR1) is a novel lncRNA with significant sequence similarity to the lncRNA steroid receptor RNA activator 1. Schmidt and colleagues reported that SLNCR1 is an abundantly-expressed lncRNA associated with worse overall survival in melanoma patients. Further functional and mechanistic characterization demonstrated that SLNCR1 increases melanoma invasion by transcriptionally upregulating matrix metalloproteinase 9 (MMP9) in cooperation with the brain-specific homeobox protein 3a (Brn3a) and the androgen receptor (AR).[61] This study may partially why males have higher incidence of melanoma metastases and exhibit an overall lower survival.[62]

2.9 | Sammson

SAMMSON is a recently annotated lncRNA with its encoding gene located on chromosome 3p13–3p14, which also harbours the melanoma-specific oncogene *MITF*.[63] Leucci and colleagues demonstrated that SAMMSON was frequently co-amplified with *MITF* and its expression is lineage-specific. Functional assays showed that exogenous SAMMSON increased the clonogenic potential of melanoma cells whereas SAMMSON knockdown drastically decreased melanoma cell viability and sensitized melanoma to MAPK-targeting therapeutics. Mechanistically, SAMMSON interacts with p32 to increase its mitochondrial localization for regulating mitochondrial

TABLE 1 Functional characterization of the lncRNAs in melanoma

lncRNAs	Expression	Functional role	Related gene	Role	References
HOTAIR	Up	Motility invasion gelatin matrix		Oncogene	[25, 26]
MALAT1	Up	Migration metastasis	miR-140 Slug ADAM10	Oncogene	[32, 33]
BANCR	Up	Migration proliferation	ERK1/2 JNK MAPK	Oncogene	[35, 42]
SPRY-IT1	Up	Proliferation differentiation apoptosis	lipin 2	Oncogene	[43, 48, 49]
ANRIL	Up	Colony formation migration	INK4A INK4B	Oncogene	[6, 57]
Llme23	Up	Malignant phenotypes	PSF Rab23	Oncogene	[58]
UCA1	Up	Migration proliferation	miR-507 FOXM1	Oncogene	[32, 60]
SLNCR1	Up	Invasion	MMP9 Brn3a AR	Oncogene	[60]
SAMMSON	Up	Viability oxidative	*MITF* MAPK	Oncogene	[63]

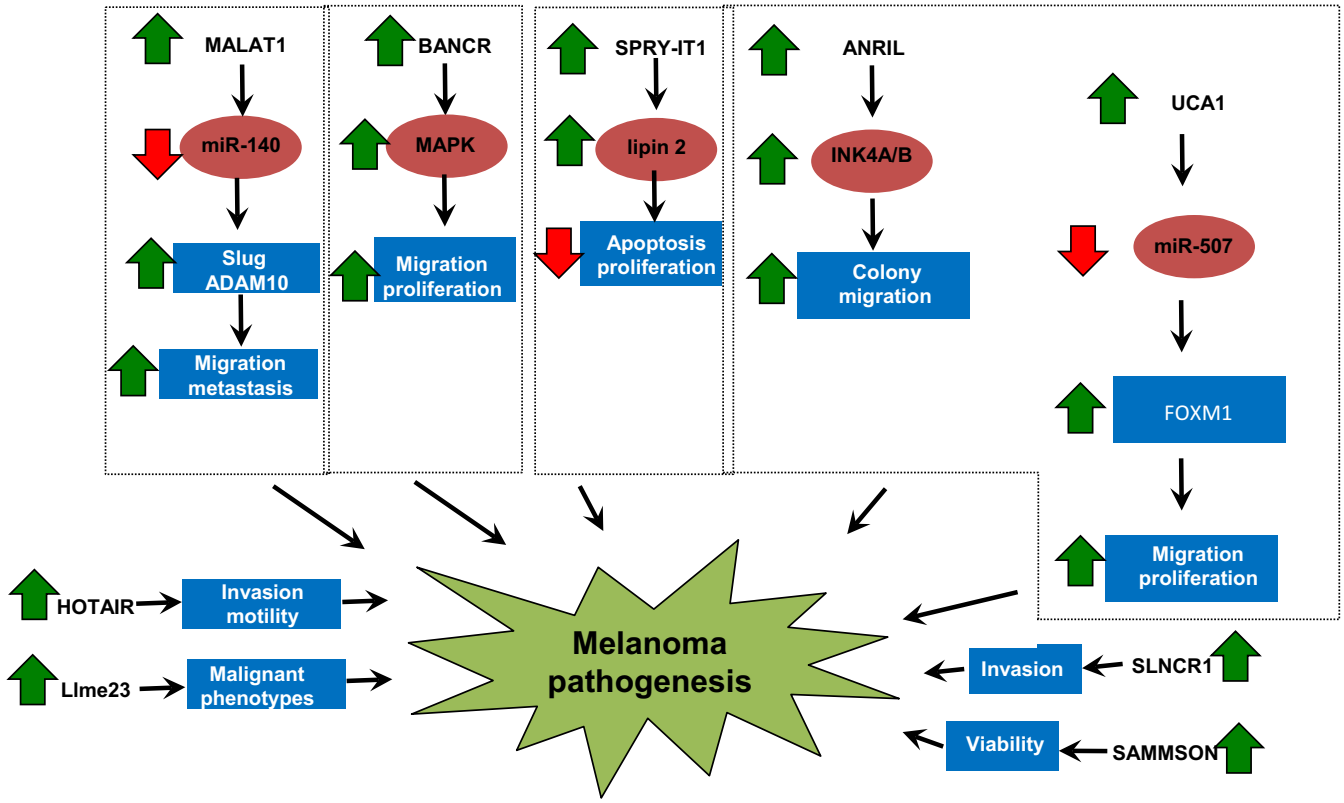

FIGURE 1 Functional roles of specific deregulated lncRNAs in melanoma

homeostasis and metabolism. Concordantly, targeting SAMMSON decreased oxidative phosphorylation, mitochondrial ribosome biogenesis, and respiratory chain complex activity in a cancer-cell-specific manner.[63] These results suggest that SAMMON silencing may deliver effective anti-melanoma therapeutic responses (Table 1 and Figure 1).

3 | CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Melanoma is the most aggressive type of skin cancer with rapid metastatic progression. Early diagnosis is crucial for melanoma management as advanced melanomas are refractory to conventional treatment and associated with dismal survival outcomes. LncRNAs were initially considered to be functionless and therefore termed "genomic dark matter". However, emerging studies have revealed their important functions. Although thousands of lncRNAs have been identified, only few have been functionally characterized. Current research has revealed the importance of lncRNA in tumourigenesis. In melanoma, several lncRNAs have been demonstrated to be differentially expressed in melanoma and function as potent regulators of melanoma progression and metastasis. These lncRNAs include HOTAIR, MALAT1, BANCR, ANRIL, SPRY-IT1, Llme23, UCA1, SLNCR1 and SAMMSON. However, the current knowledge of lncRNAs in terms of their deregulation and mechanisms in melanoma is far from complete. Moreover, the clinical utilities of lncRNAs remain not fully established. Future investigations are therefore needed to clarify the upstream and downstream mechanisms as well as clinical implications of lncRNA deregulation in melanoma.

CONFLICTS OF INTEREST

The authors declare no competing financial interests.

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