Perspective

# Role of the lncRNAs in malignant melanoma and their involvement in metastasis

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**Abstract:** Malignant melanoma is an aggressive disease and its incidence is still rising. Despite available targeted therapies the prognosis of patients with advanced disease is relatively poor. Therefore, detailed understanding of the mechanisms that lead to melanoma development and characterization of the underlying molecular events associated with the outcome is essential for a more effective therapy. The molecular and cellular biology of melanomas involves a complex network of multiple factors interacting with different signaling pathways and disrupting the gene regulatory mechanisms. Recently, the long non-coding RNAs (lncRNAs) were identified as new transcriptional regulators modulating gene expression at various levels and playing an important role in diverse biological processes including carcinogenesis, tumor development and progression. Several lncRNAs have been shown to provide potential prognostic markers and represent novel therapeutic targets in different cancers. Aberrant expression of lncRNAs are frequently observed in various cancers including melanomas. However, studies investigating lncRNAs in malignant melanoma are limited and their potential or functional role in driving metastatic progression in particular is largely unknown. A recent report has revealed a mechanism by which the lncRNAs might mediate metastasis in melanoma. The study provided evidence that the lncRNA growth-arrest specific transcript 5 (GAS5) can modulate the metastatic capacity of melanoma cells by suppressing expression of the matrix metalloproteases MMP2 and MMP9. It was shown that knocking down GAS5 resulted in upregulation of the MMPs which may facilitate new therapeutic implications. In this article the current understanding on the role of lncRNAs and the associated functional mechanisms in melanoma pathogenesis and their involvement in promoting metastases are evaluated.

**Keywords:** Long non-coding RNA (lncRNA); melanoma; growth-arrest specific transcript 5 (GAS5); metastasis

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Malignant melanoma originates from the melanocytes and is the most aggressive type of skin cancer. Although it accounts for approximately 1% of the cutaneous tumors the disease is responsible for more than 70% of the deaths from skin cancer (1). In contrast to the declining incidence of most tumors, incidence of malignant melanoma has been rising at a rate of 3% over the past 25 years (2). The majority of the patients are diagnosed at early stages when the disease is in a curable state. However, the 5-year survival rate decreases to 63% in patients with regional metastases and it is only 16% in patients with distant metastases (3).

Malignant melanoma comprises a heterogenous group of tumors that harbor different somatic mutations in key cellular genes controlling multiple signaling pathways (4). Melanomas developing at different sites of the body may display different biological and clinical characteristics. Recent studies have shown that melanomas have one of the highest rates of somatic mutations of all solid tumors (5). The underlying molecular heterogeneity indicates that different mechanisms are involved in the etiology of the disease (6).

Recently, the development of high-throughput sequencing technologies have enabled genome-wide evaluation of the molecular changes and provided insight into the molecular heterogeneity and pathogenesis of melanomas.

Genetic predisposition is a known risk factor for melanoma and accounts for 10% of the cases. Disruptions in several principal signaling pathways such as Ras/Raf/MAPK, PI3K/Akt, JAK/STAT, MITF and JNK that control the cell cycle, proliferation, differentiation and apoptosis have been associated with the development of malignant melanoma (7). *BRAF* is the most frequently mutated gene in melanoma. Activating mutations of the *BRAF* gene are present in more than 70% of melanomas and the *BRAF* V600E mutation constitutes almost 90% of these (8). *BRAF* V600E and *NRAS* mutations are mutually exclusive in newly diagnosed melanomas but during disease progression *NRAS* mutations develop in the tumors of 25% of patients harboring the V600E mutation (9).

## Long non-coding RNAs (lncRNAs)

Although most of the human genome is transcribed at some point during the lifespan, only 1.9% of the genome codes for proteins (10). Most of this transcriptional activity is mainly due to the transcription of the non-coding RNA molecules, the majority of which are lncRNAs. lncRNAs are defined as a class of non-protein coding RNA molecules larger than 200 nucleotides (11). When compared with the small non-coding RNAs the abundance of the lncRNA transcripts far exceeds the small RNAs with recent estimates of more than 30,000 transcripts (12). The ubiquity and diversity of the lncRNAs indicate that they exert important regulatory functions. Conservation of the lncRNAs during evolution and strict mechanisms controlling their expression indicate that lncRNAs are essential for a variety of biological processes (13).

lncRNAs act as transcriptional regulators and can modulate gene expression at various levels by interacting with cellular DNA, proteins and other RNA molecules (14). They may guide regulatory proteins to the promoter sites or can prevent these from binding to the promoters activating or silencing target genes, participate in the cross-talk with the miRNAs, alternative splicing and nuclear import, and act as precursors to small RNAs or as decoys for proteins (14-17). lncRNAs can recruit protein complexes to specific genomic loci (18) and many lncRNAs may also exert additional functions in the cytoplasm during translation of the rRNAs (19).

With such diverse modes of action and functional consequences lncRNAs play important roles in carcinogenesis (11,20) and recent evidence suggests that aberrations in the lncRNA expression are associated with the development of various tumors (21). Studies of lncRNAs in different cancer types have shown that lncRNAs may function as tumor promoters or suppressors (16-22) and are also associated with metastasis and therapeutic response (23-25). Furthermore, studies investigating the utility of lncRNAs in predicting prognosis have also provided promising results (26).

Expression of lncRNAs are more tissue specific than protein coding genes supporting the distinct functions of these molecules in different tissues (27). Advances in the next-generation sequencing technologies had an enormous impact on medical research enhancing the capacity to identify, characterize and investigate the aberrations in individual tumors. Data from recent whole genome and transcriptome studies have revealed that lncRNAs display altered expression patterns in different cancers including melanomas. Several studies have associated lncRNA molecules with the etiology and development of melanoma (28-32). However, association of lncRNAs with metastases in melanoma is not well defined since very few studies have addressed this issue.

A study published recently pointed to a possible mechanism by which lncRNAs may contribute to the development of metastases in malignant melanoma and confirmed the fact that lncRNA expression patterns may vary between species as well as between different cell lines from the same cancer type (33).

In the following sections the current knowledge on the roles of lncRNAs in malignant melanoma will be summarized.

## lncRNAs in malignant melanoma

An initial study analyzing differential expression of lncRNAs in normal melanocytes, melanoma cell lines and primary tumors has identified a candidate lncRNA that might be involved in the transition from the normal melanocyte into melanoma (28). This paper was followed by a report investigating expression of lncRNAs in *BRAF*-mutated tumors which revealed novel lncRNA transcripts with potential clinical relevance driven by the *BRAF* V600E mutation (29).

The first lncRNA characterized by these studies was the 687 bp lncRNA SPRY4 transcript (SPRY4-IT1), derived from an intron of the *SPRY4* gene which is upregulated in

 

melanoma (28). Suppression of SPRY4-IT1 was shown to result in abnormal cell growth or differentiation, increased apoptosis rates and decreased invasion capacity of melanoma cell lines (28,34). Presence of typical regulatory sequences (nested helices, pyknons) in its structure suggest that these regions may play a role in post-transcriptional gene silencing, and indicate that SPRY4-IT1 may also exert direct effects on gene expression (35). It has been suggested that SPRY4-IT1 may play a regulatory role in the pathogenesis of melanomas and even act as an early biomarker (36). Although the cellular function of SPRY4-IT1 is not clear a recent study has shown that SPRY4-IT1 controls the epithelial-mesenchymal transition in non-small cell lung cancer by modulating E-cadherin and vimentin expression leading to cell proliferation and metastasis (37).

The 1,600 nucleotide human lncRNA Llme23 binds directly to the polypyrimidine tract-binding protein-associated splicing factor (PSF) and was reported to play an oncogenic role in human melanoma driving the malignant properties and tumor formation (32). PSF can interact with the regulatory regions of several target oncogenes repressing their expression. Llme23 is exclusively expressed in human melanoma cell lines and was found to inhibit the tumor suppressing activity of PSF (38). It was shown that downregulation of Llme23 suppresses the malignant characteristics of the melanoma cells by repressing expression of the RAB23 protooncogene (39).

A screen of differentially expressed lncRNAs in *BRAF* V600E mutated melanoma cells has led to the identification of the 693 bp lncRNA transcript, *BRAF*-activated non-coding RNA (BANCR) (29). BANCR is overexpressed in malignant melanoma and was shown to induce tumor proliferation by activating the MAPK and JNK pathways. Knockdown of BANCR in melanoma cells results in migration defects and significant reduction of motility, indicating an important role of BANCR in the regulation of melanoma cell motility (14,29). The effect of BANCR on motility is thought to occur by a positive feedback mechanism with the V600E mutation inducing BANCR overexpression which then stimulates upregulation of the chemokines (35). Expression of BANCR increases with tumor stage and melanoma patients with high BANCR expression were shown to have a poor prognosis (40).

The HOX transcript antisense RNA (HOTAIR) was identified by its overexpression in metastatic melanomas and lymph node metastases compared to primary tumors (30). In contrast to most of the other lncRNAs cellular functions of HOTAIR are relatively well-defined. HOTAIR is transcribed from the *HOXC* cluster and interacts with the polycomb repressive complex 2 (PRC2) suppressing and silencing transcription of the *HOXD* cluster (41). It is thought to regulate gene expression at hundreds of different genomic loci by interacting with the PRC and LSD1 complexes (42). HOTAIR also directs PRC2 to specific targets, inducing H3K27 methylation, H3K4 demethylation and leading to epigenetic silencing of the metastasis suppressor genes (43). Aberrant HOTAIR expression is observed in different cancer types including breast, lung, colon, liver and pancreas cancers and in ovarian and gastrointestinal stromal tumors (35).

The lncRNA ANRIL was identified by mapping of the *INK4/ARF* locus in a melanoma-nerve tumor family. Recent GWAS data associating a polymorphic variant of ANRIL with melanoma risk suggest that ANRIL is associated with melanoma pathogenesis (44). ANRIL is involved in the control of cell proliferation by regulating *CDKN2A/B* expression and has been associated with several cancer types. The important role of the *CDKN2A/B* locus in melanoma implies that ANRIL might affect the susceptibility and participate in melanoma progression although its mechanism remains to be studied.

Data from SNP arrays have shown that melanoma-specific amplifications detected on chromosome 3p harbor a recently identified lncRNA (45). SAMMSON is the target of the lineage-specific transcription factor SOX10 and promotes survival of the melanoma cells. SAMMSON expression is detected in more than 90% of melanomas but not in other tissues (46). Further analysis of 60 different cell lines and 24 different tumor types have shown that SAMMSON is selectively expressed in melanomas (45). Knockdown of SAMMSON inhibits growth of invasive melanoma cells and enhances the effect of MEK and *BRAF* inhibitors even in cells with acquired resistance providing a new therapeutic target (47).

RMEL3 is another lncRNA specific for melanoma. Its expression is significantly increased in melanomas when compared to other tumors (48). RMEL expression promotes cell proliferation and survival by stimulating the activity of the MAPK and PI3/Akt pathways. A close connection between the *BRAF* V600E mutation and higher RMEL3 expression has also been reported (49).

Another lncRNA acting as a transcriptional regulator in melanomas is the MIR31HG molecule which plays role in cellular senescence and has been reported to suppress $p16^{INK4}$ expression in melanoma (50).

 

## Role of lncRNAs in metastasis

Numerous studies investigating the role of lncRNAs in cancer indicate that they can participate in cellular processes leading to the development of metastases (35,51). Recent data suggest that several lncRNAs may induce or promote metastasis in a cancer type-specific manner (35). However, analysis of lncRNAs which have been correlated with metastasis in different cancers has shown that these were not associated with the development of metastasis in malignant melanoma (23-25,30,35).

Several studies have revealed that HOTAIR expression is important for the development of metastases. Pro-metastatic activity of HOTAIR has been shown in different cancers including breast (23), pancreatic (52) and hepatocellular carcinoma (25). In metastatic melanomas HOTAIR expression is markedly upregulated. Knockdown of HOTAIR results in significant loss of invasiveness and a marked decrease in the metastatic activity of melanoma cells (30) while the matrix metalloproteinases are upregulated (53).

## Growth-arrest specific transcript 5 (GAS5)

The GAS5 is an intriguing tumor suppressor lncRNA that plays crucial roles in the regulation of apoptosis and cell proliferation in different types of cancers (54-57). GAS5 was identified using a cDNA library and derives its name from the fact that its expression increases in response to growth arrest induction (58). The gene is located at 1q25 and consists of 12 exons which are alternatively spliced to yield two possible mature lncRNAs, GAS5a and GAS5b (59). Transcription of GAS5 is controlled primarily by the mammalian target of rapamycin (mTOR) pathway but the nonsense-mediated decay (NMD) pathway can also induce GAS5 expression (60,61).

The GAS5 lncRNA exerts its function primarily by binding directly to the DNA-binding domain of the glucocorticoid receptor and preventing the receptor from interacting with its response element thereby repressing transcription of the target genes that suppress apoptosis (62).

A second mechanism of action is inhibition of miR-21 expression by specific lncRNA-miRNA interaction. It has been shown that GAS5 and miR-21 can mutually suppress expression of each other suggesting a feedback between the two molecules (63). Inhibition of miR-21 by GAS5 leads to the release of the tumor suppressor genes targeted by miR-21 inducing apoptosis and suppressing cell proliferation. Recently, description of miR-222 as another target of GAS5 supports this mechanism (64).

In addition to these functions GAS5 can also regulate target genes by direct binding. It has been shown to bind to and negatively regulate translation of the *c-MYC* mRNA and other transcription factors (65).

GAS5 acts a tumor suppressor in breast cancer and GAS5 levels are significantly lower in the breast tumors compared with normal tissue (60). Downregulation of GAS5 has been reported in renal cell carcinoma (66), bladder cancer (67), prostate cancer (68), pancreatic cancer (57) and colon cancer (69). Moreover, suppression of GAS5 expression has been found to correlate with tumor size and advanced disease in lung (56), gastric (54), colon (69) and cervical (70) cancers and was reported to provide an independent prognostic factor in hepatocellular carcinoma (71).

GAS5 has been associated with metastasis in lung (56), liver (20,71), prostate (72) and cervix (70) tumors and was shown to block the migration and invasion of liver and renal carcinoma cells (71,73). On the other hand, conversely, patients with high GAS5 expression were reported to have a high risk of liver metastases and GAS5 was suggested to represent a prognostic biomarker to predict the risk of liver metastases for early stage colon cancer (20).

The recent study by Chen *et al*. (33) identified GAS5 as a critical player associated with the inhibition of tumor growth and suppression of metastasis in five different melanoma cell lines. The study reveals that the tumor suppressive effect of GAS5 may be the result of the downregulation of the proteolytic MMPs. The mechanism described in the report is supported by the upregulation of the MMPs in response to HOTAIR inhibition (53). This finding suggests a novel mechanism by which lncRNAs participate in the regulation of cellular metastasis and warrants new studies to exploit the potential and utility of GAS5 and similar lncRNA transcripts in the development of new therapeutic approaches for the treatment of advanced melanoma cases. Differences in the expression levels in various melanoma cell lines still leaves an interesting area open for investigation. An increased understanding of the cellular mechanisms and identification of the molecular changes that lead to metastasis development will reveal new approaches for earlier diagnosis, more effective treatment and a better prognosis for the patients with melanoma.

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