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# Unraveling Long Non-Coding RNAs in Melanoma: Exploring New Frontiers for Diagnosis and Treatment

Maanya Venkat

Inglemoor High School, 15500 Simonds Rd NE, Kenmore, Washington, 98028, USA; maanyavenkat@gmail.com

ABSTRACT: Melanoma is a brutal skin cancer characterized by its complex properties and high risk of metastasis. Currently, chemotherapy, radiation therapy, and immunotherapy are the most common forms of treatment, however, the persistent rise in melanoma cases and emerging drug resistance underscore the urgency for further effective treatments. Long non-coding RNAs (lncRNAs), once considered 'transcriptional noise', have demonstrated diagnostic and therapeutic biomarker capabilities and salient epigenetic properties to target genes associated with melanoma metastasis and drug resistance. A literature review of 50+ articles from journals and databases, including *Nature*, *Frontiers*, and the *National Library of Medicine*, yielded a combined analysis of the impact of lncRNAs on melanoma diagnosis and therapies. LncRNAs were found to have roles in numerous cellular processes, showcasing their involvement in disease growth and their ability to work, augmenting the effects of current therapies, and ensuring the prevention of melanoma recurrence in the patient. This literature review aims to provide a comprehensive overview of melanoma, examine the functions of lncRNAs in cancers and melanoma, and explore future directions for leveraging lncRNAs to enhance metastatic melanoma treatments and diagnosis.

KEYWORDS: Biomedical and Health Sciences, Genetics and Molecular Biology of Disease, Melanoma Diagnosis and Therapies, Long Non-Coding RNAs.

## Introduction

Melanoma, a highly aggressive skin cancer, has seen a staggering 41% increase in melanoma cases globally from 2012 to 2020. The American Cancer Society estimated that in 2021 alone, the US would have about 106,110 new melanoma cases, along with 7,180 deaths, highlighting the ever-urgent need for effective therapies.[1,2] Despite significant advancements in cancer research, current treatments still face the inevitable risk of acquired resistance, resulting in a lack of efficacy. Within the realm of non-coding RNAs, the classification of long non-coding RNAs demonstrates key roles in gene expression regulation, influencing numerous biological processes at a cellular level, including the occurrence and development of diseases such as cancers like melanoma.[3,4] Spanning data from over 50 articles from reputable journals, including *Nature, the International Journal of Molecular Sciences, the National Library of Medicine*, and more, this review aims to explore the current diagnostic and therapeutic approaches for melanoma while investigating how the functions of lncRNAs can improve melanoma treatment and diagnosis strategies.

### *1. Malignant Melanoma:*

Melanoma is a skin cancer resulting from mutations in melanocytes. It mainly affects Caucasians, with common physical characteristics of blue eyes, fair or red hair, pale skin complexion, sunburn history, and freckles.[5,6] In comparison to the Black population, Caucasians have 20 times the risk of melanoma.[2] If not identified in early stages, the melanoma becomes metastatic, resulting in unfortunate prognoses, continued progression of the disease, and increased resistance to therapies.[1,5] To treat cancer, understanding the potential causes of development can help identify drugs to target the appropriate factors. Currently, three main factors act in tandem to determine melanoma development, as further demonstrated by **Table 1**.

**Table 1:** This table showcases the risk factors and etiology currently known for melanoma. The three main factors include exposure to ultraviolet radiation, atypical mole syndrome, especially with family history, and genetic factors, including gene mutations.

| Risk Factor | Description |
|---|---|
| Lifetime Ultraviolet Radiation | Highly energetic UVB rays (5% of Earth-reaching UV rays) damage DNA in melanocytes in the epidermis, leading to melanoma.[7] |
| Atypical Mole Syndrome | Also known as dysplastic nevus syndrome, involves abnormal nevi. Carries a 10.7% melanoma risk, increasing to 100% with family history.[6] |
| Genetics | Family history raises melanoma risk by 2.2 times. 5-10% of patients have a family history. Mutations in genes like CDKN2A, BRAF, and CDK4 are prevalent.[1,2,6,8] |

### *1.1 Melanoma Diagnosis:*

To ensure a quick and accurate diagnosis of melanoma, the mnemonic ABCDEF allows both doctors and individuals at home to catch potential cancerous lesions in the early stage, smoothing the diagnosis process exemplified by **Figure 1**. Once a suspicious lesion is identified, an excisional biopsy is typically conducted. After obtaining the results from the biopsy, doctors will look at the blood count, chemistry panel, and lactate dehydrogenase levels to determine the melanoma progression and type.[9]

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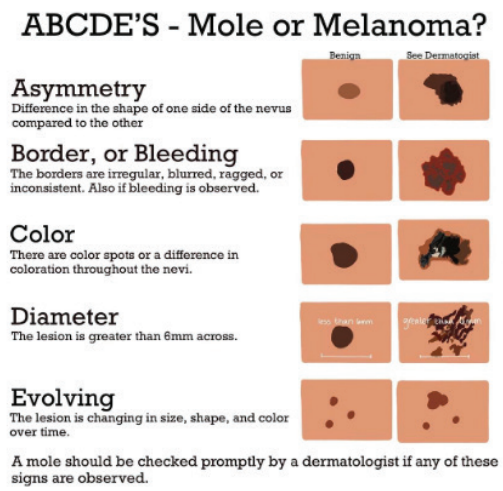


**Figure 1:** A visual representation of the ABCDE mnemonic that dermatologists use to quickly identify melanoma in a patient. Sometimes, the letter F is also included to represent family history.[9] Copyright 1993-2024, Berman Skin Institute.

### *1.2 Melanoma Subtypes:*

Continuing to build an understanding of melanoma diagnosis, exploring the four main subtypes of melanoma can showcase their differing presentation and progression. **Figures 2-5** showcase the physical properties of each subcategory and provide a detailed description of the statistics and prognosis for each melanoma subtype.

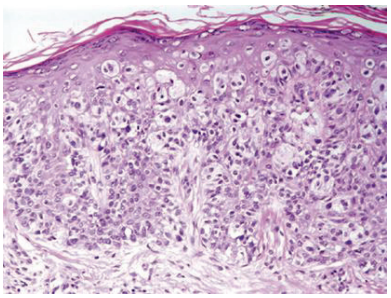

**Figure 2:** Accounting for over 75% of melanomas, **Superficial Spreading Melanoma** involves unrestricted, singular melanocytes that cause structural modifications in the epidermis with a pagetoid spread.[2,6,10] Superficial Spreading is highly curable, but only when caught early in the progression.[11] Copyright 2006, Bruce R. Smoller, United States & Canadian Academy of Pathology.

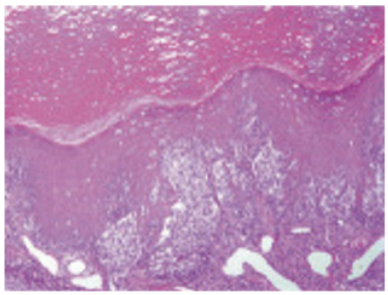

**Figure 3: Nodular Melanoma**, found in middle-aged adults, has sharply circumscribed tumor edges. Rapid vertical growth and metastasis occur after cancerous melanocytes enter the dermis, resulting in a poor prognosis.[2,6,10] If diagnosed early, it can be cured. However, due to its rapid growth, it is often found at an advanced stage.[12] Copyright 2006, Bruce R. Smoller, United States & Canadian Academy of Pathology.

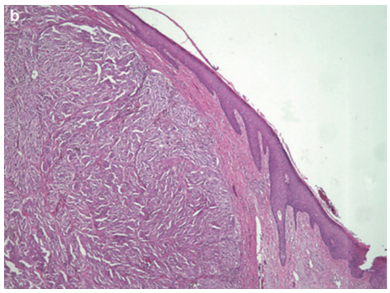


**Figure 4: Lentigo Maligna Melanoma**, primarily occurring from sun damage, typically forms on the head and neck of elderly people due to small hyperchromatic melanocytes clustering at the dermal-epidermal junction.[2,6,10] If diagnosed early, it can be cured, however, it is often confused with benign sun damage, potentially causing misdiagnosis.[13] Copyright 2006, Bruce R. Smoller, United States & Canadian Academy of Pathology.

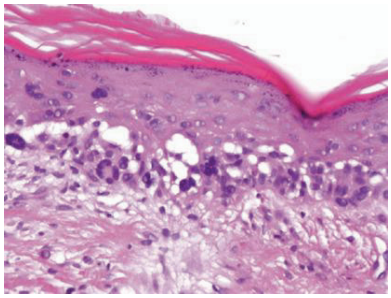

**Figure 5: Acral Lentiginous Melanoma** is rare and often diagnosed late since it is typically found under the nailbeds It features hyperchromatic melanocytes, both singular and nested, at the dermal-epidermal junction with extensive pagetoid spread.[2,6,10] This is the only melanoma not associated with sun damage and is easily curable if diagnosed early.[14] Copyright 2006, Bruce R. Smoller, United States & Canadian Academy of Pathology.

### *1.3 Current Melanoma Therapies:*

For all subtypes, a high chance of curability is associated with diagnosis and treatment early in the progression of melanoma. Currently, there are three common therapies available to treat melanoma. Before any drugs or treatments are initiated, the cancerous tumor is surgically removed. To increase the overall survival rates, adjuvant therapy is given afterward, such as immunotherapy or targeted therapy. Immunotherapies, such as PD-1 and PD-L1 inhibitor therapies, which suppress T-cell activation, have positive outcomes, with their main role in reducing the occurrences of metastasis.[1,5,9] However, melanoma recurrence is common, as the immune system develops an acquired drug resistance, failing to recognize the T-cells that destroy the cancerous cells. Targeted therapy is a second option as it silences mutated genes in association with melanoma. However, it is still relatively new, and 50% of cases develop acquired resistance to this therapy as well. In cases where the melanoma is too advanced, chemotherapy is the preferred option; Dacarbazine is the standard chemotherapy drug for melanoma. Though it is an important palliative treatment and there are improved clinical responses, there isn't necessarily an improved overall survival for the patient, as the drug could ultimately develop resistance to cellular apoptosis, causing a reappearance of the melanoma.[1,5] In conclusion, a therapy where drug resistance doesn't occur and can effectively kill melanoma is necessary to see improved survival among growing melanoma cases.

### *2. Long non-coding RNAs:*

Long non-coding RNAs (lncRNAs), found in the nucleus and cytoplasm of cells, are a classification of RNA greater than 200 nucleotides long without protein-coding abilities. Initially, lncRNAs were thought to have seemingly little to no biological function, due to a lack of expression and sequence conservation, but research proved that hypothesis wrong.[3,15]

### *2.1 Understanding and Targeting LncRNAs:*

LncRNAs have been found to have important regulatory functions at epigenetic, transcriptional, and post-transcriptional levels due to their complex structure and mechanisms for expression regulation. Hence, they are also closely related to the occurrence, development, and prevention of diseases, including cancer, and play roles in other cellular processes such as the cell cycle, differentiation, and metabolism.[15,16]

#### *2.1.1 Modes of Action:*

LncRNAs have four main molecular modes, or functions, of action. In *signal* mode, the lncRNAs function as enhancers in gene imprinting, thereby changing the chromatin architecture, attracting transcriptional proteins to promote target gene transcription, and influencing signaling pathways under specific conditions. In contrast, in *decoy* mode, lncRNAs act as a decoy to block molecular pathways and suppress pre-apoptotic genes. They bind to proteins with transcriptional regulatory functions and control the activity of molecules and signaling pathways to regulate the activation and inhibition of transcription-related genes. *Guide* mode enables lncRNAs to interact and bind with chromatin-modifying enzymes to direct them to a specific local gene for its activation or repression. Lastly, *scaffold* mode, similar to guide, interacts with RNA-binding factors and proteins to form RNA-protein complexes, which either promote or suppress transcription by recruiting proteins to target the promoter region or by binding to existing gene suppressors. **Figure 6** showcases a visual representation of the above information.[3,17-21] An additional mode, *sponging*, allows lncRNAs to act as "molecular sponges" by binding to microRNAs (miRNAs), preventing their interactions with target mRNAs.[22] **Figure 7** showcases this in a visual representation.

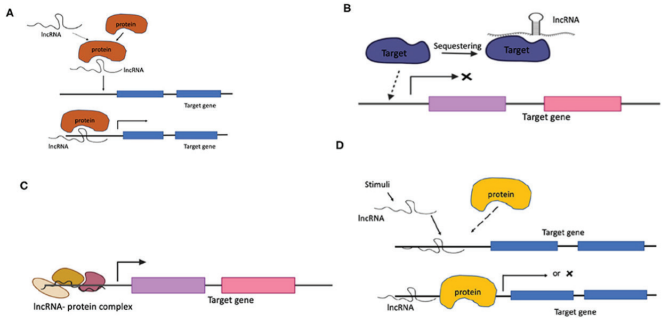


**Figure 6:** Main modes of action present in lncRNAs. (A) In *signal* mode, the lncRNA interacts with a protein to relay cellular signals to the target gene; (B) The lncRNA sequesters the target enzyme, preventing it from interacting with the target gene in *guide* mode; (C) In *decoy* mode the lncRNA-protein affects the transcription of the target gene; (D) The lncRNA acts as a stimulus for the protein to affect transcription of the target gene in *scaffold* mode.[18] Copyright 2021, Chowdhary *et al.* Luxembourg Centre for Systems Biomedicine.

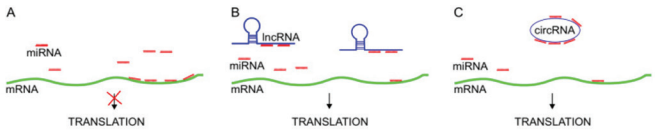


**Figure 7:** LncRNA sponging pathway. (A) miRNAs bind to the region of target transcriptions to block translation; (B/C) lncRNAs or circRNAs overpower the miRNA, resulting in the resumed translation.[22] Copyright 2021, Wozniak and Czyz, Department of Molecular Biology of Cancer, Medical University of Lodz.

#### *2.1.2 LncRNA-Targeting Biotechnologies:*

LncRNAs' modes of action can be targeted to downregulate or upregulate depending on their specific functions. Technologies including antisense oligonucleotides (ASOs), RNA interference (RNAi), and clustered regularly interspaced short palindromic repeats (CRISPR) can be used to aid in the process. ASOs are single-stranded nucleic acids that specifically target lncRNAs and siRNAs for silencing. RNAi uses the cells' own mechanisms for downregulation, and CRISPR can remove lncRNAs entirely.[23] ASOs, specifically, target lncRNAs by degrading lncRNA transcripts. One study using nude mice showed that *in vivo* injected ASOs can inhibit lncRNAs, in this case MALAT1, to block metastasis.[24] With the current knowledge of lncRNA modes of action and overall epigenetic functions, these technologies could be significant in the pursuit of effective cancer therapies utilizing lncRNAs.

### *2.2 LncRNAs in Cancers:*

While continuous research for cancer has led to numerous therapies and diagnosis processes, cancer cases continue to rise on the path to surpassing heart diseases, according to the 2016 American Cancer Statistics Report.[25]

#### *2.2.1 Biomarker Potential:*

The use of tumor markers for early diagnosis was identified in 1978. As of right now, tumor antigens, specifically carcinoembryonic antigens (CEAs), glycoproteins, and ectopic hormones, are the most commonly used clinical tumor markers.[25,26] However, due to their extensive applications as a marker, they have a risk of misdiagnosis or the inadvertent neglect of certain markers. Recently, lncRNAs have been discovered as biomarkers for early cancer diagnosis, showing promising results.[25]

LncRNAs such as TINCR (Terminal differentiation-induced non-coding RNA), BANCR (BRAF-activated non-protein coding RNA), and CCAT2 (Colon cancer-associated transcript 2) can be detected from a patient's plasma and function as biomarkers to identify gastric cancer.[18] Exosomal lncRNAs and circulating lncRNAs are promising lncRNAs for oncologists. In addition to their importance in the cell cycle, regeneration, etc., they are involved in tumor growth, metastasis, angiogenesis, and chemoresistance. They are present in bodily fluids, allowing for a plentiful supply.[25,26] Circulating lncRNAs (circRNAs) regulate melanoma growth, invasion, and immune evasion, can stably exist in the circulatory system, and can also be found in bodily fluids. In a study of 32 blood samples from both gastric cancer and healthy patients, the circRNA H19 was expressed more in cancer patients, with-


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out any evidence of age or race affecting the result; circRNA expression can act as a biomarker. Additional studies showed that the circulating lncRNA MALAT-1 (metastasis-associated lung adenocarcinoma transcript 1) was upregulated in numerous cancer tissues, including but not limited to lung and prostate cancer. MALAT-1 can determine the presence of lung cancer with 96% specificity and prostate cancer with 84.8% specificity.[26] HOTAIR is another lncRNA involved in many carcinogenic processes and is related to the resistance of cisplatin, an antineoplastic agent. It can therefore be a potential biomarker in different cancer cells, such as breast, gastric, colorectal, and cervical cancer cells.[27] Circulating lncRNAs, including H19, HOTAIR, and GACAT2 (gastric cancer-associated transcript 2), have been shown to outperform glycoprotein biomarkers with greater cancer diagnostic performance.[26] Overall, due to their immense involvement in cellular processes and carcinogenesis, lncRNAs have great potential to be used as more widespread biomarkers for diagnosis.

The diverse functions of lncRNAs showcase their incredible potential to be important markers or supplementary treatments in the future. Their established biomarker potential in other cancer types, including gastric cancer, lung cancer, and more, strengthens the thesis that lncRNAs can aid in the early diagnosis of melanoma as well as better curability probabilities. Additionally, with the help of biotechnologies created for gene modification, such as CRISPR and RNAi, lncRNAs could be significant in the fight against drug resistance with current therapies.

### *3. LncRNAs in Melanoma:*

Out of a study using a collection of over 7000 RNA sequencing libraries, 339 lncRNAs were associated with melanoma.[28] LncRNAs can be targeted differently depending on their subtype and functions, be it oncogenic or tumor suppressing, to hold potential for new diagnosis and treatments.

### *3.1 Functionally Relevant lncRNAs in Melanoma:*

A high frequency of lncRNAs prevalent in melanoma are overexpressed, boosting cell proliferation and tumorigenesis.[32] These lncRNAs are oncogenic, as they promote cell growth through the activation of cellular pathways involved in processes like angiogenesis, genomic instability, invasive metastasis, and chemotherapy resistance.[33] Some of the most common oncogenic lncRNAs include H19, SAMMSON, BANCR, HOTAIR, and MALAT1, all of which are upregulated. H19 specifically was the first lncRNA found to be associated with tumorigenesis.[34] Many of these also have sponging abilities and are able to indirectly or directly interact with miRNAs, acting as competing endogenous RNAs (ceRNAs), a specific classification of lncRNAs.[35] Given that oncogenic lncRNAs are a significant group of cellular process regulators and are expressed differently in malignant melanocytes, they have the potential to be biomarkers and used as adjuvant gene therapy to boost the efficacy of current treatments.

A second classification of lncRNAs, tumor suppressors, is downregulated in melanoma and contributes to tumor onset and progression. These lncRNAs can impact regulators in the cell cycle, specifically regulating the expression of tumor suppressor genes to affect proliferation, genomic stability, and apoptosis.[36] Common melanoma-specific tumor suppressor lncRNAs include MEG3 and LINC00961. Many of them specialize in sponging, emphasizing their tumor suppression roles.[22, 28-30] Their abilities to affect cell proliferation, metastasis, growth cycle, and apoptosis highlight promising utilization, especially as a biomarker for melanoma.[29] For further details on the functions and the regulation of specific oncogenic and tumor suppressor lncRNAs, see **Table 2**.

**Table 2:** This table highlights the main functions and the impact of the regulation of melanoma-specific oncogenic and tumor suppressor lncRNAs. Note: This is not a comprehensive list; only 14 lncRNAs out of many lncRNAs were picked. Additionally, it is important to note that lncRNAs that express both oncogenic and tumor suppressor functions are only found in certain conditions.[33] That said, most of those express oncogenic functions, so that was showcased in the table. * = not explicitly stated in article(s); inferred based on descriptions of lncRNA.

| lncRNA | Oncogenic/Tumor Suppressor | Mode of Action | Function | Regulation in Melanoma |
|---|---|---|---|---|
| **BANCR** | Oncogenic/Both (ceRNA)[28,32,33] | Sponging[32,37] | BRAF-activated nonprotein coding RNA[28] | Silencing downregulates the MAPK signaling pathway restricting tumor growth and metastasis[28] |
| **CASC2** | Tumor Suppressor (ceRNA)[28,32] | Sponging[32] | Promotes tumor growth inhibitor RUNX[22, 28-29] | Downregulated in melanoma; re-expression inhibits melanoma proliferation[22, 28,29] |
| **H19** | Oncogenic/Both (ceRNA)[32,33,38] | Sponging (NF-κB pathway), decoy*, signal* [32,39] | Affects melanoma cell growth, metastasis, invasion, and apoptosis; involved in stemness[29,40] | Downregulation regulates signaling pathways restricting melanoma growth[29] |
| **HOTAIR** | Oncogenic (ceRNA)[27,28,35] | Sponging (miR-152-3p)[41] | HOTAIR and miR-152-3p sponging suppresses target gene c-MET and activates a signaling pathway to promote melanoma metastasis and growth; involved in chemoresistance[40] | Upregulation of miR-152-3p after the silencing of HOTAIR allowed for lowered cell growth[41] |
| **ILF3-AS1** | Oncogenic (ceRNA)[32,38] | Guide* (EZH2 interactions)[42] | Involved in the proliferation and invasion of melanoma cells[52] | Upregulated in melanoma; High levels of ILF3-AS1 corelated with metastasis and poor prognosis. Silencing inhibits cell proliferation[42] |
| **LINC00961** | Tumor Suppressor (ceRNA)[28,29,43] | Sponging[43] | Downregulated in melanoma; restriction of cell proliferation, encouragement of apoptosis[22,28-30] | Overall survival with high Linc00961 levels was significantly higher than those with low levels[28,29,43] |
| **MALAT1** | Oncogenic/Both (ceRNA) [32,33,38] | Sponging* (miR-23a)[32,44] | Promotion of cell proliferation and migration through miR-23a; involved in angiogenesis[40] | Downregulation of MALAT1 inhibited cell proliferation, migration, expression[44] |
| **MEG3** | Tumor Suppressor (ceRNA) [28,29,31,32] | Sponging[31,32,45] | Suppression the growth and pro-apoptosis functions in melanoma[31] | Downregulated in melanoma; low levels of MEG3 were positively correlated with poor prognosis[45] |
| **MIR31HG** | Oncogenic[46] | Guide[46] | Upregulated in melanoma; lowered expression of p16INK4A tumor suppressor protein, increased melanoma proliferation[46] | Silencing promotes cellular aging/senescence in the melanoma cells[46] |
| **NKILA** | Tumor Suppressor (ceRNA)[32,38] | Decoy* (NF-κB pathway)[32,47] | Inhibition of melanoma invasion and metastasis[28-30] | Downregulated in melanoma; expression triggers apoptosis and reduces melanoma invasion[50] |
| **SAMMSON** | Oncogenic[3] | Scaffold* (p32) and Decoy* (CARF protein)[30] | Involved in mitochondrial metabolism, protein translation, and signaling pathways such as Wnt and MAPK[8,30] | Overexpressed in melanoma; silencing weakens the mitochondria's membrane, lessening melanoma survival rate[8,30] |
| **SLNCR** | Oncogenic[32] | Guide[32,46] | Promotes p21 expression and contributes to oncogenesis[46] | High levels associated with worse overall survival of melanoma; downregulation significantly decrease melanoma invasion[48] |
| **SPRY4-IT1** | Oncogenic[32] | Sponging[32,51] | From the intronic region of SPRY4 gene, associated with BRAF[29] | Silencing induces apoptosis in melanoma[29] |
| **UCA1** | Oncogenic (ceRNA)[32,38] | Sponging, Decoy* [8,32] | Promotes melanoma proliferation and invasion through miR-28-5p and miR-507 axes; involved in cell migration and invasion[8,40] | Inhibition of UCA1 expression reduces melanoma cell migration and proliferation; miR-28-5p expression significantly reduced[49] |

### *3.2 LncRNA-based Diagnostic and Treatment Applications:*

Currently, lncRNA-based therapies aren't approved for clinical use. However, they are predicted to be crucial in addressing drug resistance and improving the overall survival of melanoma patients as diagnostic and therapeutic targets.

#### *3.2.1 Diagnostic Potential:*

LncRNAs have gained attention as diagnostic biomarkers in melanoma for their roles in the regulation and expression of biological processes. Currently, biopsies and physical examinations are the most reliable diagnostic tests for melanoma; however, differentiating between benign and malignant melanocytes can be difficult. LncRNAs would aid as a supplementary biomarker test to further simplify diagnosis.[53] LncRNAs present in melanoma, such as lncRNAs H19, HOTAIR, MEG3, and TUG1, are a few key targets.[54] Though for lncRNAs to be effective diagnostic markers, they should be easily detectable and stable in plasma or other bodily fluids, enabling noninvasive diagnosis.[4]

### *3.3 Therapeutic Potential:*

Rather than a stand-alone treatment, lncRNAs would potentially be used in tandem with current therapies and technologies to increase the chance of overall patient survival.

#### *3.3.1 Immunotherapy:*

Immunotherapy, which currently utilizes immune checkpoint inhibitors to enhance T-cell immune responses, lacks efficacy.[29] One recent immunotherapy is the use of PD-1 (programmed cell death protein 1) to treat tumors and to predict patient survival rates. LncRNAs derived from the PD-L1 (PD-1 ligand) gene sites encourage the transcriptional activity of the c-Myc signaling pathway, promoting the growth of cancerous cells. Silencing these lncRNAs and blocking the immune checkpoints could result in tumor suppression. However, despite the potential of immune therapies like anti-PD-1, over half of patients experience drug resistance.[55]

Mechanisms such as the overexpression of the histone methyltransferase EZH2 in melanoma are linked with poor prognosis and affect resistance to the anti-PD-1 treatment.[55] Interestingly, recent studies suggest that tumor-infiltrating immune-related lncRNAs (Ti-lncRNAs) have a higher efficacy rate than the anti-PD-1 treatments when melanoma patients' Ti-lncRNA levels are low.[29] About 15 lncRNAs, including NARF-AS1 and LINC01126, are able to predict prognosis of those treated with anti PD-1. Conversely, lncRNAs, including HOTTIP, IFITM4P, and LINC01140, upregulate PD-L1 expression in melanoma and increase immune cell immune escape.[29, 53] Overall, integrating lncRNAs alongside immunotherapies could enhance their efficacy and restrict resistance challenges.

#### *3.3.2 Targeted Therapy:*

Recent studies have linked lncRNAs with BRAF mutations: a significant therapeutic target, affecting over 60% of melanoma patients.[29] Though many BRAF inhibitors (BRAFi) such as vemurafenib and dabrafenib have been approved and widely accepted clinically, resistance to the BRAFi develops after a median time progression-free survival of 9 months.[57, 58] Researchers hypothesize that the repeated exposure of BRAFi stabilizes the modified epigenome in melanoma cells, leading to resistance, assuming such modifications are reversible.

Using this hypothesis, researchers at the University of Colorado Boulder in the Department of Biochemistry conducted a study by treating thousands of singular melanoma cells utilizing BRAFi dabrafenib and observed their reaction over the first four days. While most cells responded positively to the treatment, within three days, a portion of cells escaped the treatment, returning to a cancerous state after drug withdrawal, resulting in acquired resistance.[55,59]

Among the lncRNAs involved in transcriptional activation, EMICERI has been identified as a key player in BRAFi resistance.[56] EMICERI becomes overexpressed following BRAFi resistance, upregulating the MOB3B (MOB kinase activator 3B) gene and downregulating the LATS1 (large tumor suppressor kinase 1) gene. This activates the Hippo signaling pathway, which is largely involved in tumor growth and metastasis due to its functions in tissue and organ growth.[22,58] Targeting EMICERI for downregulation could reduce the effects of the BRAFi resistance, inhibiting further melanoma proliferation.

Another study, conducted by researchers at the VIB-KU Leuven Center for Cancer Biology observed injections of lncRNA SAMMSON antisense nucleotides in mice, which resulted in significant tumor suppression, both independently and with exposure to dabrafenib. However, when dabrafenib was combined with trametinib, the mice endured increased tumor growth. The study determined that SAMMSON would act as a biomarker and a highly selective therapeutic target.[22,60]

In conclusion, lncRNAs such as SAMMSON and EMICERI have proven to significantly aid in overcoming BRAFi resistance, offering promising futures for increased overall patient survival.

Though lncRNAs have not yet been applied to clinical settings, their numerous functions in oncogenic, tumor suppressor, and epigenetic processes highlight their significant potential as biomarkers and adjunctive therapies to address drug resistance and enhance drug efficacy in metastatic melanoma. The extensive studies and research into their prospective implementation within immunotherapies and targeted therapies underscores the promise of lncRNAs in advancing more effective treatments for patients globally.

## ■ Conclusion

Through this paper, the critical role of lncRNAs in melanoma diagnosis and treatments, focusing primarily on metastasis and drug resistance, has been thoroughly examined. With versatile functions, ranging from diagnostic biomarkers to influencing key cellular processes, including the cell cycle and apoptosis, lncRNAs have proven to present a fascinating and promising pathway for the future of melanoma treatment and diagnosis. Not only can they improve treatment efficacy, but they can also prevent the recurrence of melanoma. Leveraging gene editing biotechnologies, such as CRISPR, can facilitate


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lncRNAs as an adjuvant targeted therapy to work alongside immunotherapies or chemotherapies. Melanoma continues to remain a formidable territory in oncology, however, continued research on lncRNAs in melanoma is paving the way for clinical implementation. As this research evolves, these molecules, once thought of as mere 'transcriptional noise', hold the potential to revolutionize melanoma care, providing innovative solutions towards the realms of personalized medication, increased patient survival, and perhaps bringing us closer to conquering this deadly cancer.

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## Author

Maanya Venkat, a junior at Inglemoor High School, was inspired to explore oncology and genetics following the loss of her family's black labrador. She plans to pursue biomedical engineering in college. Outside of academics, Maanya enjoys tennis, music performance, and working at the local veterinary clinic.