Molecular Therapy
Oncolytics
Review

Non-coding RNAs in melanoma: Biological functions and potential clinical applications

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Malignant melanoma (MM) is a malignant tumor that originates from melanocytes and has a high mortality rate. Therefore, early diagnosis and treatment are very important for survival. So far, the exact molecular mechanism leading to the occurrence of melanoma, especially the molecular metastatic mechanism, remains largely unknown. Non-coding RNAs (ncRNAs), such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNA (circRNAs), have been investigated and found to play vital roles in regulating tumor occurrence and development, including melanoma. In this review, we summarize the progress of recent research on the effects of ncRNAs on melanoma and attempt to elucidate the role of ncRNAs as molecular markers or potential targets that will provide promising application perspectives on melanoma.

INTRODUCTION

Melanoma is the most aggressive and lethal type of skin cancer. It originates from melanocytes and has a poor prognosis.[1,2] According to clinical factors and molecular characteristics, melanoma can be divided into four subtypes: cutaneous melanoma with chronic sun damage, cutaneous melanoma without chronic sun damage, acral melanoma, and mucosal melanoma.[3,4] In white people, the main subtypes of melanoma are non-acral cutaneous melanomas, and the prevalence of acral melanomas and mucosal melanomas is only about 5% and 1%, respectively.[5,6] In the Asian population, the main subtypes of melanoma are acral melanoma and mucosal melanoma, which account for more than 70% of the melanoma in this population.[7]

Recent statistics show that the incidence of melanoma is increasing at an annual rate of 5%.[8] Although it accounts for less than 10% of skin malignancies, the mortality rate is as high as 80%.[9] The main reasons for the high mortality rate are that melanoma has a high degree of malignancy, rapid progress, and the existing treatments are not ideal. Patients can have local lymph node and distant organ metastases at an early stage. There are various ways to diagnose and treat melanoma clinically. At present, the most effective treatment is early diagnosis, enlarged resection, and lymph node dissection.[10] Because a significant number of patients have metastasized when they are diagnosed, the prognosis is poor and the 5-year survival rate is less than 20%.[8] In recent years, however, with the clinical application of targeted therapy and immunotherapy, some patients have benefited greatly, especially from targeted therapies such as BRAF (B-Raf proto-oncogene, serine/threonine kinase; vemurafenib) and mitogen-activated protein kinase kinase (MEK) (trametinib) inhibitors.[11–13] However, due to subtype bias, more than 50% of Asian patients are unable to benefit from targeted therapy of BRAF and c-Kit; because the tumor gene mutation load in this population is low, the overall mutation frequencies of BRAF and c-Kit are about 25.5% and 10.8%, respectively.[14,15] In addition, recent clinical studies have shown that immunotherapy with anti-cytotoxic T lymphocyte-associated protein 4 (CTLA4) or anti-programmed cell death 1 (PD1) antibodies provides promising clinical benefits for some melanoma patients, but drug resistance remains.[16–18] Therefore, it is vital to find new melanoma-specific markers and anti-tumor drug targets in the field of melanoma research.

Non-coding RNAs (ncRNAs), which account for 98% of the human genome, are a type of RNA without protein coding functions, which mainly include microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs).[19] Although ncRNAs do not have the function of encoding proteins, they can regulate physiological processes such as DNA replication, RNA transcription, and protein translation, and they play an important role in cell differentiation and metabolism. They are widely involved in regulating the occurrence and development of tumors by playing the role of a proto-oncogene or tumor suppressor gene.[20–23] In recent years, there has been an increase in research focused on exploring the role of multiple ncRNAs in regulating the proliferation, migration, angiogenesis, recurrence, and metastasis of malignancies, including melanoma.[24,25] In this review, we discuss recent studies on the role of miRNAs, lncRNAs, and circRNAs in melanoma. Moreover, we provide an overview of the current knowledge of the relationship between ncRNAs and melanoma as well as the potential impact and promise of ncRNAs in the diagnosis and treatment of melanoma.

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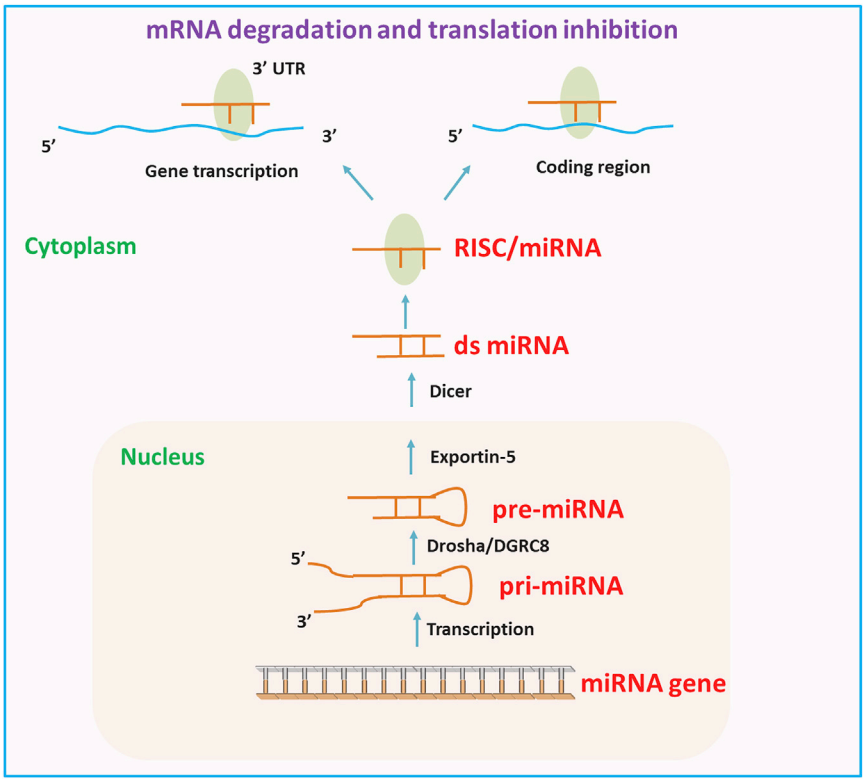

Figure 1. The process of miRNA biogenesis and miRNA in gene regulation

A miRNA is transcribed from its gene into pri-miRNA, which is cut into a pre-miRNA by Drosha. Pre-miRNA is transported to the cytoplasm through exportin 5/Ran-GTP and is cleaved by Dicer into a miRNA-miRNA duplex. The leader strand is loaded onto the RISC, and then the target mRNA is inhibited on the 3′ UTR.

BIOLOGICAL CHARACTERISTICS AND FUNCTIONS OF ncRNAs

With the advancement of human genomics and the rapid development of next-generation sequencing technology, researchers have found that only about 1.5% of the nucleic acid sequences in the human genome are related to protein coding, and the rest are called ncRNAs because they do not encode proteins.[26] ncRNAs mainly include ribosomal RNA (rRNA), transfer RNA (tRNA), miRNA, lncRNA, circRNA, and competitive endogenous RNA (ceRNA). Among these ncRNAs, miRNA, lncRNA, and circRNA have been widely reported to play important roles in the occurrence and development of tumors.[27–29] miRNAs are a type of endogenous non-coding small RNA with a length of about 18–24 nt. Most miRNAs are processed from either miRNA DNA or introns. The miRNA sequence is transcribed to the primary transcript primary miRNA (pri-miRNA), which is additionally capped and polyadenylated by RNA polymerase II. The pri-miRNA is then cut into a precursor miRNA (pre-miRNA) by Drosha in the nucleus. Next, exportin 5 and Ran-guanosine triphosphate (GTP) bind the pre-miRNA and thus enable its export from the nucleus into the cytoplasm. In the cytoplasm, the pre-miRNA is cleaved into a mature double-stranded, ~22-nt miRNA/miRNA duplex processed by Dicer. The double-stranded miRNA complex then binds to the RNA-induced silencing complex (RISC). Functional miRNA is produced after the complementary strand is removed from the RISC and degraded. Its function is mainly by combining with the RISC to form the miRISC complex and then specifically binding to the mRNA encoding the protein, causing degradation of the target mRNA or inhibiting its translation, thereby regulating gene expression at the post-transcriptional level (Figure 1).[30–32] lncRNAs are a type of ncRNA with transcripts longer than 200 nt. They can compete with miRNAs, DNAs, or transcription factors to act as a "molecular sponge" and can cause upregulation or downregulation of target protein expression. lncRNAs are able to recruit or prevent the binding of the transcriptional elements and transcription factors, directly impacting the transcriptional output. lncRNAs are also involved in post-transcriptional regulation in the nucleus. For example, lncRNAs can interact with the splicing machinery or directly with nascent RNAs to guide particular splicing patterns. In the cytoplasm, lncRNAs can influence translational output in different ways. First, they can regulate the translational rate by modulating polysome loading to an mRNA molecule or controlling the internal ribosomal entry sites. In addition, they can also regulate gene expression by reducing or stimulating mRNA decay (Figure 2).[33–35] circRNAs are a novel endogenous ncRNA with a special covalent closed loop structure, which does not have a 5′ end cap and 3′ end poly(A) tail structure. circRNAs may arise from introns or exons, which result in the formation of different types of circRNAs, that is, exonic, intronic, and exon-intron circRNAs. The exonic circRNA is the result of pre-mRNA splicing. When the 3′ splice donor is attached to the 5′ splice acceptor, the exonic circRNA is formed. If the introns between exons are retained, the resulting circular transcription is called exon-intron circRNA. Intronic circRNAs can be produced by intronic lariats, which can resist degradation by debranching enzymes. Their function can be used as a miRNA sponge, regulating alternative splicing and gene transcription, protein translation, and the ceRNA mechanism (Figure 3).[36–38]

miRNAs IN MELANOMA

miRNAs are a type of key molecules in post-transcriptional regulation of genes, involved in cell proliferation, differentiation, and the occurrence and development of various diseases.[39,40] Different studies have demonstrated that more than 60% of human genes are regulated by miRNAs, which might act as oncogenes or tumor suppressors, depending on target gene, cellular context, and tissue.[41–43] Several

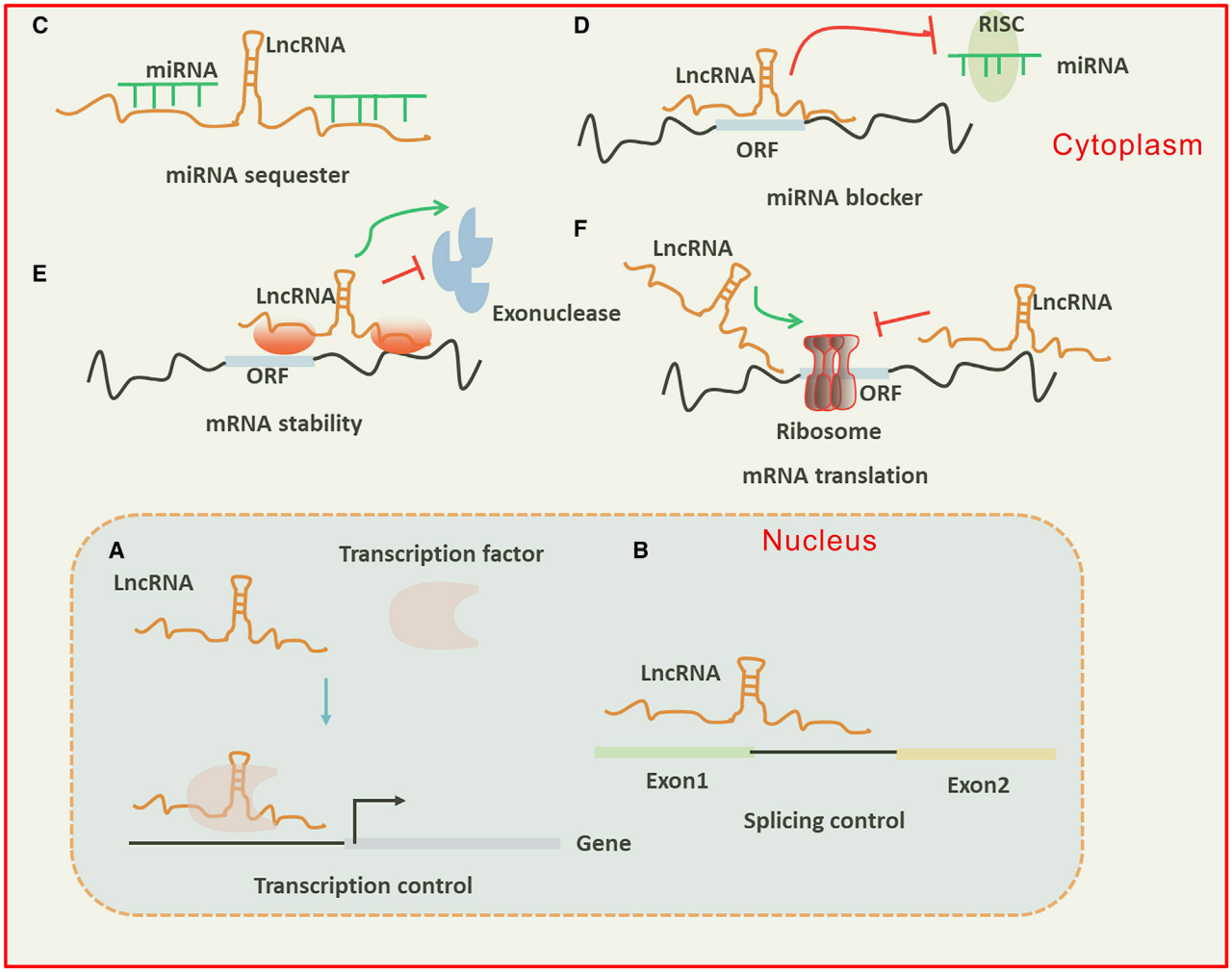

Figure 2. Models of lncRNA functions

(A) lncRNAs activate transcription of some genes by recruiting transcription factors to their enhancers or promoters and suppress transcription by secluding transcription factors and keeping them away from their enhancers or promoters. (B) lncRNAs can regulate mRNA functioning through base pairing with them and altering their splicing patterns. (C and D). lncRNAs can act as "sponges" by base pairing with their complementary miRNAs and inhibiting their effects. Cytoplasmic lncRNAs can regulate mRNA expression by competing for microRNA binding or blocking miRNA. (E and F) lncRNAs can regulate mRNA expression by regulating mRNA stability or mRNA translation by base pairing with mRNA molecules in the cytoplasm.

miRNAs have oncogene or tumor suppressor activities and play a key role in cancer development, progression, and matastasis.[44] Abnormal miRNA expression has been found in many human tumors, including breast cancers, hepatocellular carcinoma, bladder cancer, and gastric and colorectal cancer, among others.[45–49] In recent years, several studies have analyzed miRNAs important involvement in proliferation, invasion, and metastasis of melanoma[50–52] (Figure 4).

miRNAs act as oncogenes in melanoma

Previous studies have confirmed that many miRNAs are involved in the development of melanoma (Table 1). miR-155 is a regulatory gene that plays a role in a variety of human cancers, including lung cancer, acute myeloid leukemia, and hepatocellular carcinoma[64–66] Peng et al.[67] found that miR-155 is upregulated in melanoma cell lines and tissues. It directly targets NDFIP1 (Nedd4 family interacting protein 1) and inhibits its expression. When NDFIP1 is downregulated, it induces the growth and migration of melanoma cells. Ling et al.[68] found that the expression of miR-367 was upregulated in melanoma tissue samples through quantitative polymerase chain reaction, and phosphatase and tensin homolog (PTEN) was its target gene. miR-367 promoted the colony formation of melanoma cells by regulating PTEN. miR-21 is a well-known modulator of cell proliferation, survival, and migration/invasion. Deregulation of miR-21 has been found in human cutaneous melanoma, and higher levels expression of miR-21correlate with advanced tumor stage, invasion, and tumor recurrence. Some studies have identified that PTEN is a direct target

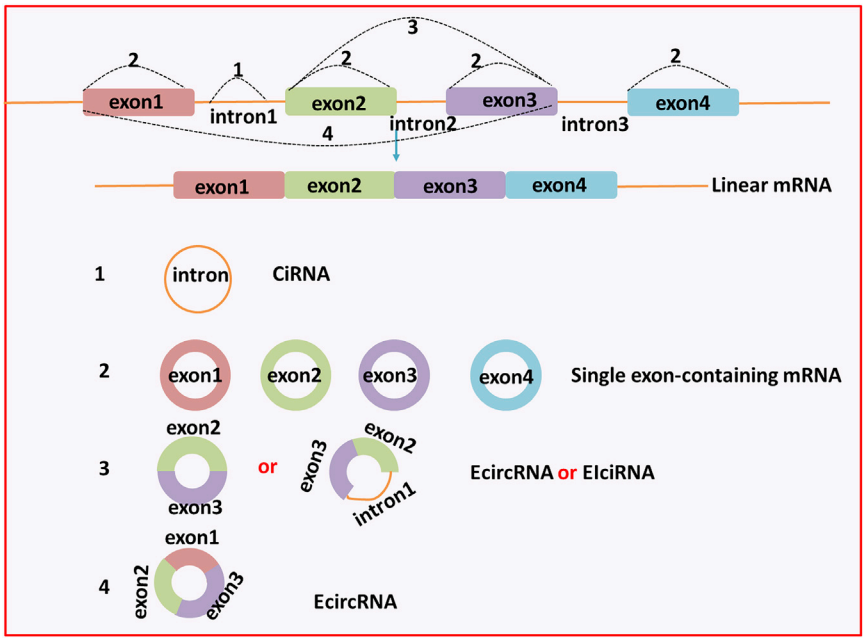

Figure 3. circRNA types are diverse

There may be many types of circRNA derived from the same gene. circRNAs are generated from the single exons of pre-mRNAs by back-splicing. Back-splicing coupled with splicing removes the intervening introns to produce exonic circRNAs (EcircRNAs). Some EcircRNAs with a retained intron are generated by back-splicing and called exon-intron circRNAs (ElcircRNAs). Some of the intron lariats produced during canonical splicing escape the debranching process and form stable intronic circRNAs (CiRNAs).

of miR-21, and levels of PTEN, in turn, regulate the activation of the phosphatidylinositol 3-kinase (PI3K)/AKT pathway.[69] In addition, some miRNAs have also been shown to affect apoptosis of melanoma cell. For example, miR-638 is significantly overexpressed in metastatic melanoma. The overexpression of miR-638 enhances the pro-tumorigenic and metastatic properties of melanoma cells *in vitro* and *in vivo*. miR-638 can also prevent melanoma cells from autophagy and apoptosis by regulating TP53INP2 expression, and it stimulates p53 and p53 downstream target gene expression.[70] Other miRNAs, such as miR-214, miR-100, and miR-125b, have been reported to be involved in the control of melanoma cell proliferation and apoptosis.[62,71] These findings suggest that miRNAs can play an oncogenic role in melanoma.

miRNAs act as tumor suppressors in melanoma

Compared with miRNAs as an oncogene, studies show that more miRNAs act as tumor suppressors. Liu et al.[72] found that miR-9 was significantly reduced in highly invasive uveal melanoma (UM) cell lines. miR-9 can negatively regulate the expression of nuclear factor κB (NF-κB) and its downstream targets such as matrix metallopeptidase (MMP)-2 and MMP-9, and of vascular endothelial growth factor A (VEGFA), thereby inhibiting the migration and invasion of uveal melanoma cells. Let-7 is the first miRNA to be shown to be involved in tumor formation. Let-7, a member of the let-7 family, plays an important role in melanoma. Schultz et al.[73] analyzed melanoma patients and found that five members of the let-7 family were significantly downregulated. Further studies found that let-7b overexpression in melanoma cells can reduce the expression of cyclin D1, cyclin D3, and cyclin-dependent kinase 4 (Cdk4), and significantly reduced the number of melanoma cells in the S phase and G_1 phase and reduced the non-adherent growth of melanoma cells. It can be seen that let-7b may negatively regulate the growth and proliferation of melanoma cells by inhibiting progression of the melanoma cell cycle. Yan et al.[74] found that miR-34a can directly or indirectly downregulate the expression of c-MET, p-Akt, and other cell cycle-related proteins in uveal melanoma, thereby significantly inhibiting tumor growth and migration. Another potent tumor suppressor miRNA, such as miR-200c, its expression is significantly reduced in melanoma cells.[75] Decreasing miR-200c increases Bmi-1 expression, which enhances the activation of the mitogen-activated protein kinase (MAPK) and PI3K/AKT pathways and the acquisition of the characteristics of the epithelial-to-mesenchymal transition (EMT), such as N-cadherin, and the upregulation of downregulation of E-cadherin.[76]

Exosome miRNAs in melanoma

Exosomes, which are the smallest type of extracellular vesicles (EVs) that are 30–180 nm in diameter, were discovered by Pan et al.[77] Tumor-derived exosomes contain abundant miRNAs (exo-miRNAs) and various enzymes that are involved in the synthesis and regulation of miRNAs, and they play a key role in epigenetic regulation.[78] In the past few years, exosomes have been considered to be predictive and prognostic biomarkers useful in monitoring tumor development and a new tool for drug delivery by acting as transporters of various significant bioactive molecules, including miRNAs, that play a key role in the intercellular crosstalk between cancer and stromal cells, promoting the maturation of the tumor microenvironment.[79–81] Melanoma-derived exosomes have been shown that can induce the migration of endothelial cells and affect angiogenesis by transporting miR-9 to endothelial cells. Moreover, exosomes can enhance metastatic niche formation in hypoxic conditions.[58,82] Rappa et al.[83] revealed 49 miRNAs with higher concentration in metastatic-melanoma derived exosomes than in primary cells by using miRNA profiling. Among them, 20 miRNAs have been proven to have a specific cancer-associated function. In addition, Xiao et al.[84] demonstrated 130 upregulated and 98 downregulated miRNAs in melanoma-derived exosomes compared with melanocyte-derived exosomes, among which 70 miRNAs, including let-7a, miR-221, and miR-31, were related to malignancy. Furthermore, the role of exosomes in

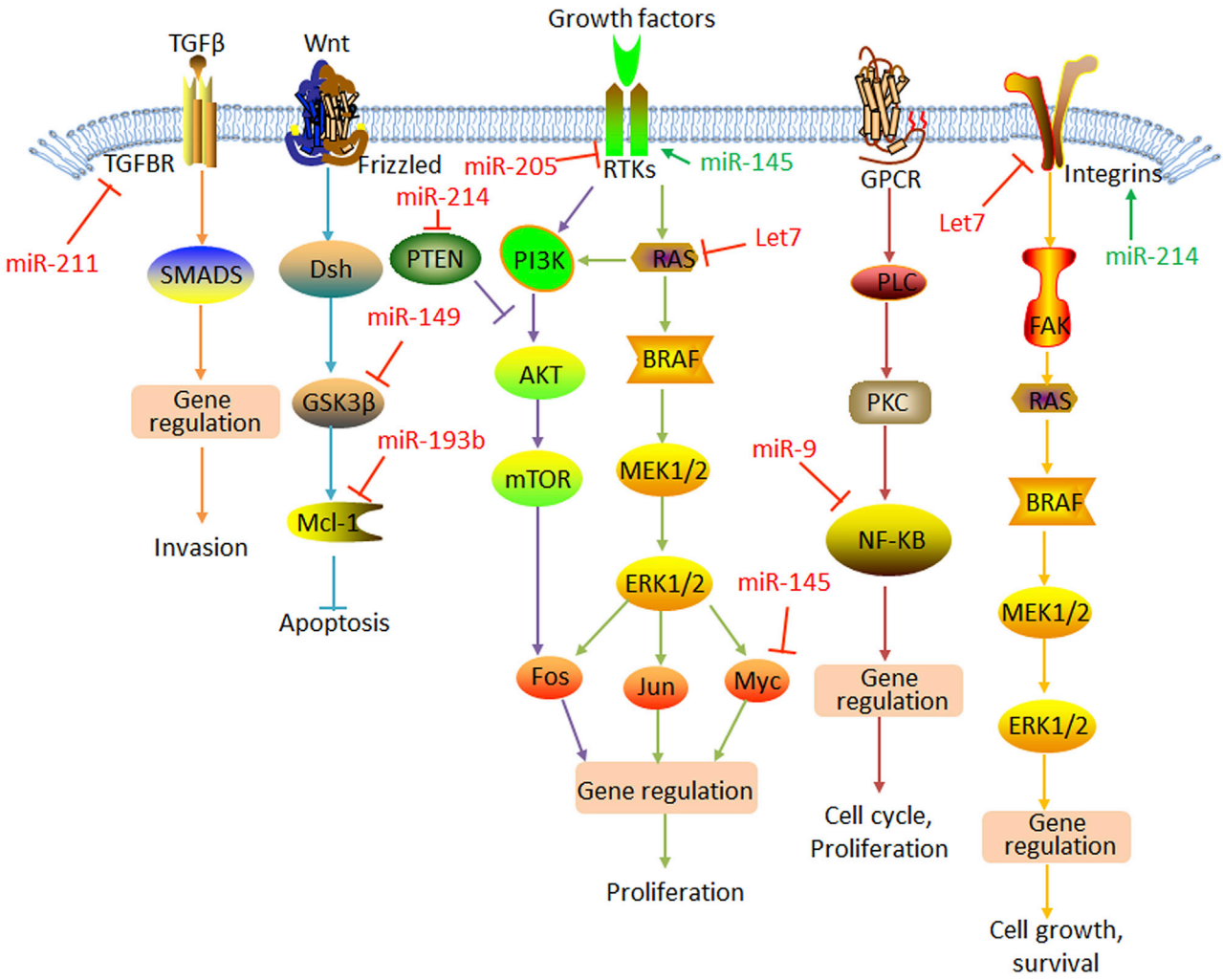

Figure 4. MicroRNAs regulate various genes and pathways in melanoma

preparing a pre-metastatic niche in distant tissues has recently been described.[85] Dror et al.[86] showed that melanoma-derived exosomes transport of miR-211 contributes to the melanoma cells crosstalk with fibroblasts. Moreover, exosomes are released into the dermis prior to melanoma cell invasion. These findings showed that melanoma cells are able to regulate the stromal niche during the early phase of melanoma.

miRNAs and immunity in melanoma

Melanoma is a well-known immunogenic cancer. Many antigens and specific lymphocytes have been isolated from melanoma.[87] The immune system plays a important role in melanoma therapy, and some specific immune therapies have been developed, such as anti-CTLA4 and anti-PD1 (ipilimumab and nivolumab/pembrolizumab, respectively)-based immune therapies, which were the first agents to be approved by the US Food and Drug Administration (FDA).[88,89] In 2014, nivolumab was approved by the FDA for metastatic melanoma treatment, and anti-PD1 antibodies have demonstrated the highest efficacy in melanoma. Notwithstanding the remarkable clinical results, most patients (50%–60%) treated with these agents do not have a durable response.[88,90] Recently, miRNAs have been investigated as regulators of this immune-evasive property of melanoma cells. It has been reported that miR-30d can mediate the inhibition of GALNT7 (*N*-acetylgalactosamine [GalNAc] transferase 7) to promote the expression of interleukin (IL)-10, which in turn triggers an immune-suppressive response.[91] Studies have shown that miR-30e can regulate the cytotoxicity of natural killer (NK) cells through targeted regulation of perforin.[92] miR-155 can also regulate the function of NK cells. Overexpressed miR-155 can increase the activity of NK cells by targeting to hematopoietic-specific inositol phosphatase 1 (SHIP-1) and promote the secretion of immune-stimulating cytokine interferon γ (IFN-γ).[93] Moreover, miR-155 is involved in modulating the IL-1β-induced downregulation of microphthalmia-associated transcription factor (MITF)-M expression in melanoma cells.[94] In addition, some miRNAs, such as miR-146, have been suggested to promote M2 polarization and generate

Table 1. The deregulated miRNAs in melanoma

miRNA	Expression	Target	Activity	Role	Reference
miR-137	down	MITF	proliferation	tumor suppressor	[53]
Let7a-b	down	integrin β3, BSG	migration, invasion	tumor suppressor	[54,55]
miR-21	up	STAT3	proliferation	oncogene	[56]
miR-205	down	E2F	proliferation, apoptosis	tumor suppressor	[57]
miR-9	down	NF-κB	angiogenesis, ECM remodeling, metastasis	tumor suppressor	[58]
miR-182	up	MITF, FOXO3	proliferation, apoptosis, cell motility, metastasis	oncogene	[59]
miR-145	down	IRS-1	proliferation	tumor suppressor	[60]
miR-124a	down	CDK4, CDK6, cyclin D2, EZH2	proliferation	tumor suppressor	[61]
miR-214	up	TFAP2C, ITGA3	cell motility, migration, metastasis	oncogene	[62]
miR-200c	down	ZEB1	EMT	tumor suppressor	[51]
miR-222	up	p27	proliferation	oncogene	[63]

negative feedback on the activation of NF-κB-related genes regulated by Toll-like receptor 4 (TLR4).[95,96] miR-200a has been shown to suppress CDK6 expression in melanoma cells. Recently, CDK4/6 inhibitors have demonstrated promising anti-tumor capabilities in melanoma.[97]

miRNAs as therapeutic approaches in melanoma

Classical treatment options include chemotherapy, radiotherapy, and immunotherapy with great limited efficacy. Although anti-PD1 or anti-CTLA4 antibodies are showing promising clinical results, emergence of resistance has already been encountered.[98] Since many miRNAs are overexpressed in melanoma, miRNA-based cancer gene therapy offers a novel therapeutic possibility of targeting multiple gene networks[99] Huynh et al.[100] has shown the influences of antisense-miR-182 in a melanoma mouse model. They observed that antisense-miR-182 can inhibit tumor growth and metastatic spread. Consistently, Wang et al.[101] showed that the inhibition of miR-573 in a murine xenograft model reduced the growth and migration of the melanoma cells. These studies demonstrated that the regulation of miRNAs could alter the expression of oncogenic or tumor-suppressing potential of their targets, eventually resulting in therapeutic effects. Thus, identification of new miRNAs as potential therapeutic targets opens new horizons in the treatment of melanoma.

DEREGULATED lncRNAs IN MELANOMA

lncRNAs are a class of RNAs whose transcripts are longer than 200 nt and do not encode proteins. Compared with miRNAs, lncRNAs have longer sequences and more complex spatial structures, and the mechanisms involved in expression regulation are more diverse and complex. lncRNAs can modulate gene expression through various mechanisms, including chromatin modification, transcriptional regulation, RNA splicing, miRNA sequestration, and translational regulation.[102–104] In the past, lncRNAs were dismissed as nonfunctional transcriptional junk.[105] However, in recent years, there has been an increase of research focused on investigating the role of multiple lncRNAs in regulating tumorigenesis, including melanoma[106] (Table 2; Figure 5).

lncRNAs regulate melanoma cell proliferation and metastasis

Read et al.[117] found that antisense ncRNA in the INK4 locus (ANRIL) can be transcripted into a noncoding RNA containing 19 exons in the opposite direction of the P15/CDKN2B/INK4B-P16/CDKN2A/INK4A-P14/ARF gene cluster. In addition, CDKN2A mutations are found in approximately 20%–40% of familial melanomas.[118] Therefore, it can be speculated that ANRIL transplants the transcripts of gene clusters through epigenetics, thereby affecting tumor cell proliferation.[119] Similar ANRIL expression can also be seen in various other malignant tumors, such as colorectal cancer and non-small cell lung cancer.[120,121] lncRNA HOXA11-AS is overexpressed in uveal melanoma tissues and cells, and it can interact with the enhancer of Zeste homolog 2 (EZH2) to inhibit the expression of its target p21 protein. In addition, it was also found that HOXA11-AS was negatively correlated with miR-124 expression. Overexpression of miR-124 can reduce the proliferation and invasion effects of HOXA11-AS.[122] In addition, MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) is the first lncRNA proven to be associated with non-small cell lung cancer, a common tumor marker to predict lung cancer metastasis, and is associated with the occurrence and development of various tumors.[123] In melanoma-related research, MALAT1 is highly expressed in melanoma, and the expression level is positively correlated with the tumor's proliferation and invasion ability. Further research found that it can be combined with miR-183 and integrin β1 (ITGB1), and interact with splicing factors (protein factors involved in the splicing process of RNA precursors).[124]

lncRNAs regulate melanoma cell apoptosis

Long-chain ncRNA SPRY4-IT1 (or SPRIGHTLY) is the first discovered and named lncRNA associated with melanoma. It is transcripted from the intron of the SPRY4 gene. In addition to melanoma, this lncRNA also plays an important role in esophageal squamous cell carcinoma, prostate cancer, glioma, and gastric cancer.[125–128] Some

Table 2. The deregulated lncRNAs in melanoma

lncRNA	Expression	Target	Location	Functions	Reference
BANCR	up	ERK1/2	cytoplasm	proliferation	107
HOTAIR	up	PRC2	nucleus and cytoplasm	migration, invasion	108
ANRIL	up	INK4	nucleus and cytoplasm	proliferation, migration	109
MALAT1	up	Slug	nucleus	migration, metastasis	110
SAMMSON	up	p32	cytoplasm	proliferation	111
PVT1	up	miR-26b	nucleus and cytoplasm	proliferation	112
SLNCR1	up	MMP9	nucleus	invasion	113
UCA1	up	FOXM1	cytoplasm	migration, proliferation	114
H19	up	EZH2	nucleus	migration	115
HOXA11-AS	up	EZH2/P21	nucleus	proliferation, invasion	116

studies have reported that SPRY4-IT1 inhibits apoptosis by combining with lipin 2 to avoid cytolipid toxicity and alter lipid metabolism processes.[129] SAMMSON was discovered because its gene sequence is very close to the MITF gene, and its sequence at 3p13-14 was specifically amplified in about 10% of melanomas. SAMMSON is regulated by the melanocyte-specific transcription factor SOX10, and its expression has been detected in more than 90% of The Cancer Genome Atlas (TCGA) primary and metastatic melanoma patients. However, unlike its neighboring oncogene MITF, the expression of SAMMSON has no difference between the invasive and proliferative melanoma phenotypes, and there is insufficient evidence to show that these two transcripts are coordinated. Regardless of the mutation status of TP53, NRAF, or BRAF, the knockout of the SAMMSON can reduce the viability of melanoma cells.[111] The knockout of SAMMSON did not reduce the expression of MITF, so it could not promote the transcription of MITF. One of its functions is closely related to p32, which is the main regulator of mitochondrial homeostasis and metabolism. SAMMSON can enhance the function of targeting mitochondria and tumorigenesis and development of p32, thereby promoting oxidative metabolism.[111] Wang et al.[130] found that lncRNA CASC2 is lowly expressed in melanoma tissues and cell lines, and high expression of CASC2 significantly inhibits the growth and invasion of melanoma cells. In addition, it was also found that CASC2 directly binds to miRNA-181a and inhibits the expression of miRNA-181a, which further inhibits the expression of its downstream apoptosis-associated protein plexin C1 (PLXNC1), thereby promoting tumor cell apoptosis.

lncRNAs as a therapeutic target for melanoma

Evaluating the function of lncRNAs usually depends on inhibiting the activity of lncRNAs (gene knockout) and observing the resulting changes in the molecular phenotype. The specific methods of downregulating lncRNAs are antisense oligonucleotides (ASOs), RNA interference (RNAi), and clustered regularly interspaced short palindromic repeats (CRISPR).[131,132] These lncRNA downregulation technologies are expected to become future melanoma treatment technologies. SAMMSON is a lncRNA that promotes the development of melanoma and is highly expressed in tumor tissues.[111,133] ASO- and RNAi-mediated SAMMSON gene knockdown reduces the number of tumor cell clones and induces melanoma cell apoptosis, and this process is not affected by the status of BRAF, NRAS, or TP53. In *in vivo* experiments, intravenous injection of SAMMSON-specific antisense oligonucleotides in a model of patient-derived tumor xenograft (PDTX) from melanoma patients can significantly reduce tumor growth. In the PDTX model, the combined application of a SAMMSON-specific ASO and a BRAF inhibitor dabrafenib can induce apoptosis, while dabrafenib alone can only inhibit tumor growth. In addition, compared with BRAF and MEK inhibitor combination therapy, BRAF inhibitor and SAMMSON-targeted ASO combination therapy showed no signs of toxicity.[111]

THE ROLE OF circRNAs IN MELANOMA

As early as 1976, circRNAs were discovered in plant viruses.[134] At that time, researchers thought that it was a product of wrong splicing and was not valued. In the following 30 years, there were only a few reports describing the presence of circular mRNA transcripts in mammals. It was not until 2012 that Salzman et al.[135] discovered that hundreds of human genes can express circRNAs using high-throughput sequencing methods, and researchers realized that the number and extensiveness of circRNAs had been underestimated before. Since then, researchers have discovered that circRNAs are not only a type of ncRNA molecule with rich expression, high stability, diversity, and conservatism, but they also play an important role in the occurrence and development of various diseases, including melanoma[136,137] (Table 3).

Characteristics and functions of circRNAs

circRNAs are a type of non-linear single-chain ncRNA. Unlike conventional linear RNAs, circRNAs lack the typical terminal structure (5′ cap structure and 3′ polyadenylation).[146] Exonuclease degrades RNA by recognizing the end of linear RNA. The lack of these structures makes circRNAs more stable than linear RNA and resistant to exonuclease R.[147] Not only that, but also studies have found that circRNAs have species specificity, tissue specificity, disease specificity, and specificity related to developmental stage.[148–150] Moreover, a gene can produce many different types of circRNA, and even some

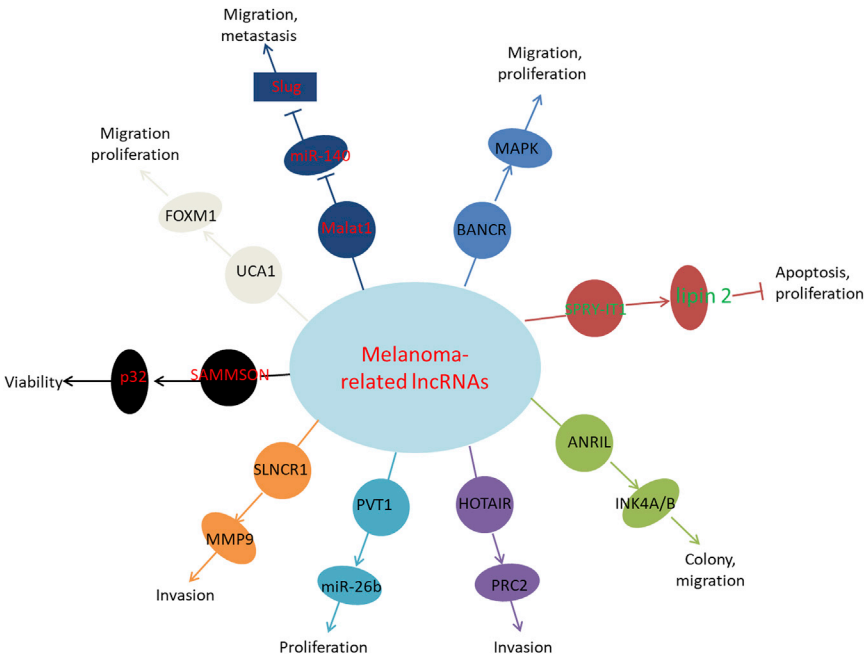

Figure 5. Deregulated lncRNAs regulate various genes and malignant phenotypes in melanoma

circRNA expression levels are more abundant than their corresponding linear RNA.

Studies have found that some circRNAs have multiple conserved miRNA binding sites that can competitively bind miRNAs to act as a miRNA sponge, and changes in circRNA abundance can regulate the effect of miRNAs on their target genes.[151] Although most circRNAs are located in the cytoplasm,[135,152] studies have shown that some circRNAs in the nucleus can regulate gene expression at the transcriptional level. For example, circRNAs can interact with U1 small nuclear ribonucleoprotein (U1snRNP), and the formed circRNA-U1snRNP complex can be combined with RNA polymerase II at the promoter of its parent gene to enhance gene expression.[147] Although most reports indicate that endogenous circRNAs cannot be combined with ribosomes for translation,[152,153] recent studies have shown that a small portion of circRNAs can encode proteins. Legnini et al.[154] found that human and mouse muscles are regulated by circZNF609 during their differentiation. This circRNA is translated into a protein in a manner that is dependent on splicing but has nothing to do with the cap structure.

circRNAs and melanoma

In recent years, more and more studies have shown that circRNAs show strong functions in regulating cell proliferation, apoptosis, angiogenesis, and metastasis, indicating that circRNAs can be used as a cancer biomarker and may be an important therapeutic target for cancer.[155] Ju et al.[156] found that many circRNAs are abnormally expressed in oral melanoma, and these circRNAs may be involved in the progression and metastasis of oral melanoma, and they may be used as a potential diagnostic biomarker for oral melanoma. Yang et al.[137] screened out seven circRNAs of expression abnormalities in uveal melanoma through bioinformatics analysis and the expression of cirRNAs constructed in the uveal MM, including hsa_circ_01119873, hsa_circ_0128533, and hsa_circ_0047924, among others, which may serve as candidates for future research on the pathogenesis of uveal melanoma. In addition, Jin et al.[141] demonstrated that human circMYC was obviously upregulated in human melanoma tissue. Furthermore, circMYC promoted the proliferation of human melanoma cells and Mel-CV cells. The expression of circMYC can repress Mel-CV cell glycolysis and lactate dehydrogenase A (LDHA) activities *in vitro*. Research by Bian et al.[145] showed that hsa_circ_0025039 is overexpressed in melanoma tissues and cell lines, which can promote tumor cell growth, invasion, and glucose metabolism through the miR-198/CDK4 axis *in vivo* and *in vitro*, suggesting that hsa_circ_0025039 may be a new target for the treatment of melanoma. The research of circRNAs in melanoma is still relatively lacking and is concentrated in the field of mucosal melanoma. Therefore, their potential as a biomarker and therapeutic target of melanoma needs to be further explored.

Table 3. The deregulated circRNAs in melanoma

circRNA	Expression	Target	Activity	Role	Reference
circ_0084043	up	miR-429	proliferation, migration and invasion	oncogene	[138]
CDR1as	down	IGF2BP3	metastasis	tumor suppressor	[139]
circ_0017247	up	miR-145	migration and invasion	oncogene	[140]
circMYC	up	miR-1236	proliferation	oncogene	[141]
circ-FOXM1	up	miR-143-3p	proliferation and invasion	oncogene	[142]
ITCH	down	GLUT1	proliferation	tumor suppressor	[143]
circ_0016418	up	miR-625	proliferation and migration	oncogene	[144]
circ_0025039	up	miR-198	invasion and metabolism	oncogene	[145]

Table 4. miRNAs, lncRNAs, and circRNAs with a diagnostic, predictive, and therapeutic role in melanoma

ncRNAs	Target	Potential clinical relevance	References
miRNAs			
miR-7	EGFR/IGF-1R/CRAF	drug-sensitive (BRAFi)	157
miR-32	MCL-1	drug-sensitive (vemurafenib)	158
miR-579-3p	BRAF, MDMD2	drug-sensitive (BRAFi/MEKi)	159
miR-125b	CCL-2	drug-resistant (vemurafenib)	71
miR-30a-5p	IGF1R	drug-resistant (cisplatin)	160
miR-206	unknown	predictive	161
miR-221-3p	unknown	prognostic	162
miR-16	unknown	prognostic	163
lncRNAs			
PICSAR	DUSP6	diagnostic	164
HOTAIR	miR-152-3p	diagnostic, prognostic	165
CASC9	Nrg1	diagnostic, prognostic	166
RMEL3	MAPK, PI3K	therapeutic target	167
LLME23	RAB23	therapeutic target	168
MALAT1	ITGB1	diagnostic, prognostic	169
circRNAs			
CDR1as	LINC00632	therapeutic target	139
circRNA_0084043	miR-153-3p	therapeutic target	170
circ_0020710	CXCL12	predictive	171
circMYC	LDHA	predictive	141
circ-GLI1	CYR61	predictive	172
circ_0002770	TGFBR1	therapeutic target	173

CONCLUSIONS

The good prognosis of melanoma still depends on early detection and early diagnosis, and targeted therapy and immunotherapy bring hope to advanced melanoma. Finding ideal biomarkers and therapeutic targets is the focus of research. Epigenetic changes are easier to discover than genetic mutations, and they are easier to reverse, which is a good breakthrough point for the early diagnosis and treatment of cancer. At present, research on melanoma has made great progress in epigenetics related to RNA, and the prospects of miRNAs, lcnRNAs and circRNAs as biomarkers are promising (Table 4). During the past decade, the explosive growth of RNA-related epigenetic research data has revealed the multi-layered complexity of gene expression and regulation. The discovery of biomarkers and refinement of therapeutic targets for melanoma is a gold mine for basic research.

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AUTHOR CONTRIBUTIONS

Q.P. assembled the related studies and drafted the manuscript. J.W. revised and finalized the manuscript. Both read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Wong, D.J., and Ribas, A. (2016). Targeted therapy for melanoma. Cancer Treat. Res. *167*, 251–262.
2. Miller, A.J., and Mihm, M.C., Jr. (2006). Melanoma. N. Engl. J. Med. *355*, 51–65.
3. Curtin, J.A., Busam, K., Pinkel, D., and Bastian, B.C. (2006). Somatic activation of KIT in distinct subtypes of melanoma. J. Clin. Oncol. *24*, 4340–4346.
4. Curtin, J.A., Fridlyand, J., Kageshita, T., Patel, H.N., Busam, K.J., Kutzner, H., Cho, K.H., Aiba, S., Bröcker, E.B., LeBoit, P.E., et al. (2005). Distinct sets of genetic alterations in melanoma. N. Engl. J. Med. *353*, 2135–2147.
5. Chang, A.E., Karnell, L.H., and Menck, H.R.; The American College of Surgeons Commission on Cancer and the American Cancer Society (1998). The National Cancer Data Base report on cutaneous and noncutaneous melanoma: A summary of 84,836 cases from the past decade. Cancer *83*, 1664–1678.
6. McLaughlin, C.C., Wu, X.C., Jemal, A., Martin, H.J., Roche, L.M., and Chen, V.W. (2005). Incidence of noncutaneous melanomas in the U.S. Cancer *103*, 1000–1007.
7. Chi, Z., Li, S., Sheng, X., Si, L., Cui, C., Han, M., and Guo, J. (2011). Clinical presentation, histology, and prognoses of malignant melanoma in ethnic Chinese: A study of 522 consecutive cases. BMC Cancer *11*, 85.
8. Foletto, M.C., and Haas, S.E. (2014). Cutaneous melanoma: New advances in treatment. An. Bras. Dermatol. *89*, 301–310.
9. Gamba, C.S., Clarke, C.A., Keegan, T.H., Tao, L., and Swetter, S.M. (2013). Melanoma survival disadvantage in young, non-Hispanic white males compared with females. JAMA Dermatol. *149*, 912–920.
10. Saranga-Perry, V., Ambe, C., Zager, J.S., and Kudchadkar, R.R. (2014). Recent developments in the medical and surgical treatment of melanoma. CA Cancer J. Clin. *64*, 171–185.
11. Flaherty, K.T., Robert, C., Hersey, P., Nathan, P., Garbe, C., Milhem, M., Demidov, L.V., Hassel, J.C., Rutkowski, P., Mohr, P., et al.; METRIC Study Group (2012). Improved survival with MEK inhibition in BRAF-mutated melanoma. N. Engl. J. Med. *367*, 107–114.
12. Sosman, J.A., Kim, K.B., Schuchter, L., Gonzalez, R., Pavlick, A.C., Weber, J.S., McArthur, G.A., Hutson, T.E., Moschos, S.J., Flaherty, K.T., et al. (2012). Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N. Engl. J. Med. *366*, 707–714.
13. Cancer Genome Atlas Network (2015). Genomic classification of cutaneous melanoma. Cell *161*, 1681–1696.
14. Kong, Y., Si, L., Zhu, Y., Xu, X., Corless, C.L., Flaherty, K.T., Li, L., Li, H., Sheng, X., Cui, C., et al. (2011). Large-scale analysis of KIT aberrations in Chinese patients with melanoma. Clin. Cancer Res. *17*, 1684–1691.
15. Si, L., Kong, Y., Xu, X., Flaherty, K.T., Sheng, X., Cui, C., Chi, Z., Li, S., Mao, L., and Guo, J. (2012). Prevalence of BRAF V600E mutation in Chinese melanoma patients: Large scale analysis of BRAF and NRAS mutations in a 432-case cohort. Eur. J. Cancer *48*, 94–100.
16. Robert, C., Schachter, J., Long, G.V., Arance, A., Grob, J.J., Mortier, L., Daud, A., Carlino, M.S., McNeil, C., Lotem, M., et al.; KEYNOTE-006 investigators (2015). Pembrolizumab versus ipilimumab in advanced melanoma. N. Engl. J. Med. *372*, 2521–2532.

17. Topalian, S.L., Hodi, F.S., Brahmer, J.R., Gettinger, S.N., Smith, D.C., McDermott, D.F., Powderly, J.D., Carvajal, R.D., Sosman, J.A., Atkins, M.B., et al. (2012). Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N. Engl. J. Med. *366*, 2443–2454.

18. Hodi, F.S., O'Day, S.J., McDermott, D.F., Weber, R.W., Sosman, J.A., Haanen, J.B., Gonzalez, R., Robert, C., Schadendorf, D., Hassel, J.C., et al. (2010). Improved survival with ipilimumab in patients with metastatic melanoma. N. Engl. J. Med. *363*, 711–723.

19. Costa, F.F. (2005). Non-coding RNAs: new players in eukaryotic biology. Gene *357*, 83–94.

20. Bartonicek, N., Maag, J.L., and Dinger, M.E. (2016). Long noncoding RNAs in cancer: Mechanisms of action and technological advancements. Mol. Cancer *15*, 43.

21. Palazzo, A.F., and Lee, E.S. (2015). Non-coding RNA: What is functional and what is junk? Front. Genet. *6*, 2.

22. Morris, K.V., and Mattick, J.S. (2014). The rise of regulatory RNA. Nat. Rev. Genet. *15*, 423–437.

23. Vidigal, J.A., and Ventura, A. (2015). The biological functions of miRNAs: Lessons from in vivo studies. Trends Cell Biol. *25*, 137–147.

24. Wang, W.T., Han, C., Sun, Y.M., Chen, T.Q., and Chen, Y.Q. (2019). Noncoding RNAs in cancer therapy resistance and targeted drug development. J. Hematol. Oncol. *12*, 55.

25. Wei, L., Wang, X., Lv, L., Liu, J., Xing, H., Song, Y., Xie, M., Lei, T., Zhang, N., and Yang, M. (2019). The emerging role of microRNAs and long noncoding RNAs in drug resistance of hepatocellular carcinoma. Mol. Cancer *18*, 147.

26. Carninci, P., Kasukawa, T., Katayama, S., Gough, J., Frith, M.C., Maeda, N., Oyama, R., Ravasi, T., Lenhard, B., Wells, C., et al.; FANTOM Consortium; RIKEN Genome Exploration Research Group and Genome Science Group (Genome Network Project Core Group) (2005). The transcriptional landscape of the mammalian genome. Science *309*, 1559–1563.

27. Huang, H., Weng, H., and Chen, J. (2020). m^6A modification in coding and non-coding RNAs: Roles and therapeutic implications in cancer. Cancer Cell *37*, 270–288.

28. Liu, X., Shao, Y., Zhou, J., Qian, G., and Ma, Z. (2020). Nuclear factor κB signaling and its related non-coding RNAs in cancer therapy. Mol. Ther. Nucleic Acids *19*, 208–217.

29. Zhang, X., Xie, K., Zhou, H., Wu, Y., Li, C., Liu, Y., Liu, Z., Xu, Q., Liu, S., Xiao, D., and Tao, Y. (2020). Role of non-coding RNAs and RNA modifiers in cancer therapy resistance. Mol. Cancer *19*, 47.

30. Liu, H., Lei, C., He, Q., Pan, Z., Xiao, D., and Tao, Y. (2018). Nuclear functions of mammalian microRNAs in gene regulation, immunity and cancer. Mol. Cancer *17*, 64.

31. Lai, E.C. (2002). Micro RNAs are complementary to 3′ UTR sequence motifs that mediate negative post-transcriptional regulation. Nat. Genet. *30*, 363–364.

32. Zhou, S.S., Jin, J.P., Wang, J.Q., Zhang, Z.G., Freedman, J.H., Zheng, Y., and Cai, L. (2018). miRNAS in cardiovascular diseases: Potential biomarkers, therapeutic targets and challenges. Acta Pharmacol. Sin. *39*, 1073–1084.

33. Sun, Q., Hao, Q., and Prasanth, K.V. (2018). Nuclear long noncoding RNAs: Key regulators of gene expression. Trends Genet. *34*, 142–157.

34. Ulitsky, I., and Bartel, D.P. (2013). lincRNAs: Genomics, evolution, and mechanisms. Cell *154*, 26–46.

35. Yao, R.W., Wang, Y., and Chen, L.L. (2019). Cellular functions of long noncoding RNAs. Nat. Cell Biol. *21*, 542–551.

36. Hansen, T.B., Jensen, T.I., Clausen, B.H., Bramsen, J.B., Finsen, B., Damgaard, C.K., and Kjems, J. (2013). Natural RNA circles function as efficient microRNA sponges. Nature *495*, 384–388.

37. Memczak, S., Jens, M., Elefsinioti, A., Torti, F., Krueger, J., Rybak, A., Maier, L., Mackowiak, S.D., Gregersen, L.H., Munschauer, M., et al. (2013). Circular RNAs are a large class of animal RNAs with regulatory potency. Nature *495*, 333–338.

38. Piwecka, M., Glažar, P., Hernandez-Miranda, L.R., Memczak, S., Wolf, S.A., Rybak-Wolf, A., Filipchyk, A., Klironomos, F., Cerda Jara, C.A., Fenske, P., et al. (2017). Loss of a mammalian circular RNA locus causes miRNA deregulation and affects brain function. Science *357*, eaam8526.

39. Mendell, J.T., and Olson, E.N. (2012). MicroRNAs in stress signaling and human disease. Cell *148*, 1172–1187.

40. Ebert, M.S., and Sharp, P.A. (2012). Roles for microRNAs in conferring robustness to biological processes. Cell *149*, 515–524.

41. Esquela-Kerscher, A., and Slack, F.J. (2006). Oncomirs—microRNAs with a role in cancer. Nat. Rev. Cancer *6*, 259–269.

42. Lewis, B.P., Burge, C.B., and Bartel, D.P. (2005). Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell *120*, 15–20.

43. Friedman, R.C., Farh, K.K., Burge, C.B., and Bartel, D.P. (2009). Most mammalian mRNAs are conserved targets of microRNAs. Genome Res. *19*, 92–105.

44. Romano, G., Veneziano, D., Acunzo, M., and Croce, C.M. (2017). Small non-coding RNA and cancer. Carcinogenesis *38*, 485–491.

45. Liu, D.L., Lu, L.L., Dong, L.L., Liu, Y., Bian, X.Y., Lian, B.F., Xie, L., Wen, D., Gao, D.M., Ke, A.W., et al. (2020). miR-17-5p and miR-20a-5p suppress postoperative metastasis of hepatocellular carcinoma via blocking HGF/ERBB3-NF-κB positive feedback loop. Theranostics *10*, 3668–3683.

46. Huang, L., Liu, Z., Hu, J., Luo, Z., Zhang, C., Wang, L., and Wang, Z. (2020). miR-377-3p suppresses colorectal cancer through negative regulation on Wnt/β-catenin signaling by targeting XIAP and ZEB2. Pharmacol. Res. *156*, 104774.

47. Noguchi, S., Yasui, Y., Iwasaki, J., Kumazaki, M., Yamada, N., Naito, S., and Akao, Y. (2013). Replacement treatment with microRNA-143 and -145 induces synergistic inhibition of the growth of human bladder cancer cells by regulating PI3K/Akt and MAPK signaling pathways. Cancer Lett. *328*, 353–361.

48. Weygant, N., Ge, Y., Qu, D., Kaddis, J.S., Berry, W.L., May, R., Chandrakesan, P., Bannerman-Menson, E., Vega, K.J., Tomasek, J.J., et al. (2016). Survival of patients with gastrointestinal cancers can be predicted by a surrogate microRNA signature for cancer stem-like cells marked by DCLK1 kinase. Cancer Res. *76*, 4090–4099.

49. Frankel, L.B., Christoffersen, N.R., Jacobsen, A., Lindow, M., Krogh, A., and Lund, A.H. (2008). Programmed cell death 4 (PDCD4) is an important functional target of the microRNA *miR-21* in breast cancer cells. J. Biol. Chem. *283*, 1026–1033.

50. Hanniford, D., Segura, M.F., Zhong, J., Philips, E., Jirau-Serrano, X., Darvishian, F., Berman, R.S., Shapiro, R.L., Pavlick, A.C., Brown, B., et al. (2015). Identification of metastasis-suppressive microRNAs in primary melanoma. J. Natl. Cancer Inst. *107*, dju494.

51. Xu, Y., Brenn, T., Brown, E.R., Doherty, V., and Melton, D.W. (2012). Differential expression of microRNAs during melanoma progression: miR-200c, miR-205 and miR-211 are downregulated in melanoma and act as tumour suppressors. Br. J. Cancer *106*, 553–561.

52. Philippidou, D., Schmitt, M., Moser, D., Margue, C., Nazarov, P.V., Muller, A., Vallar, L., Nashan, D., Behrmann, I., and Kreis, S. (2010). Signatures of microRNAs and selected microRNA target genes in human melanoma. Cancer Res. *70*, 4163–4173.

53. Chen, X., Wang, J., Shen, H., Lu, J., Li, C., Hu, D.N., Dong, X.D., Yan, D., and Tu, L. (2011). Epigenetics, microRNAs, and carcinogenesis: functional role of microRNA-137 in uveal melanoma. Invest. Ophthalmol. Vis. Sci. *52*, 1193–1199.

54. Fu, T.Y., Chang, C.C., Lin, C.T., Lai, C.H., Peng, S.Y., Ko, Y.J., and Tang, P.C. (2011). Let-7b-mediated suppression of basigin expression and metastasis in mouse melanoma cells. Exp. Cell Res. *317*, 445–451.

55. Müller, D.W., and Bosserhoff, A.K. (2008). Integrin β_3 expression is regulated by let-7a miRNA in malignant melanoma. Oncogene *27*, 6698–6706.

56. Yang, C.H., Yue, J., Pfeffer, S.R., Handorf, C.R., and Pfeffer, L.M. (2011). MicroRNA miR-21 regulates the metastatic behavior of B16 melanoma cells. J. Biol. Chem. *286*, 39172–39178.

57. Dar, A.A., Majid, S., de Semir, D., Nosrati, M., Bezrookove, V., and Kashani-Sabet, M. (2011). miRNA-205 suppresses melanoma cell proliferation and induces senescence via regulation of E2F1 protein. J. Biol. Chem. *286*, 16606–16614.

58. Zhuang, G., Wu, X., Jiang, Z., Kasman, I., Yao, J., Guan, Y., Oeh, J., Modrusan, Z., Bais, C., Sampath, D., and Ferrara, N. (2012). Tumour-secreted miR-9 promotes

endothelial cell migration and angiogenesis by activating the JAK-STAT pathway. EMBO J. *31*, 3513–3523.

59. Segura, M.F., Hanniford, D., Menendez, S., Reavie, L., Zou, X., Alvarez-Diaz, S., Zakrzewski, J., Blochin, E., Rose, A., Bogunovic, D., et al. (2009). Aberrant miR-182 expression promotes melanoma metastasis by repressing FOXO3 and microphthalmia-associated transcription factor. Proc. Natl. Acad. Sci. USA *106*, 1814–1819.
60. Li, Y., Huang, Q., Shi, X., Jin, X., Shen, L., Xu, X., and Wei, W. (2014). MicroRNA 145 may play an important role in uveal melanoma cell growth by potentially targeting insulin receptor substrate-1. Chin. Med. J. (Engl.) *127*, 1410–1416.
61. Chen, X., He, D., Dong, X.D., Dong, F., Wang, J., Wang, L., Tang, J., Hu, D.N., Yan, D., and Tu, L. (2013). MicroRNA-124a is epigenetically regulated and acts as a tumor suppressor by controlling multiple targets in uveal melanoma. Invest. Ophthalmol. Vis. Sci. *54*, 2248–2256.
62. Penna, E., Orso, F., Cimino, D., Tenaglia, E., Lembo, A., Quaglino, E., Poliseno, L., Haimovic, A., Osella-Abate, S., De Pittà, C., et al. (2011). MicroRNA-214 contributes to melanoma tumour progression through suppression of TFAP2C. EMBO J. *30*, 1990–2007.
63. Garofalo, M., Di Leva, G., Romano, G., Nuovo, G., Suh, S.S., Ngankeu, A., Taccioli, C., Pichiorri, F., Alder, H., Secchiero, P., et al. (2009). *miR-221&222* regulate TRAIL resistance and enhance tumorigenicity through PTEN and TIMP3 downregulation. Cancer Cell *16*, 498–509.
64. Ji, J., Xu, M., Tu, J., Zhao, Z., Gao, J., Chen, M., Song, J., Zhu, H., Cheng, X., Hui, J., et al. (2016). miR-155 and its functional variant rs767649 contribute to the susceptibility and survival of hepatocellular carcinoma. Oncotarget *7*, 60303–60309.
65. Ramamurthy, R., Hughes, M., Morris, V., Bolouri, H., Gerbing, R.B., Wang, Y.C., Loken, M.R., Raimondi, S.C., Hirsch, B.A., Gamis, A.S., et al. (2016). miR-155 expression and correlation with clinical outcome in pediatric AML: A report from Children's Oncology Group. Pediatr. Blood Cancer *63*, 2096–2103.
66. Xue, X., Liu, Y., Wang, Y., Meng, M., Wang, K., Zang, X., Zhao, S., Sun, X., Cui, L., Pan, L., and Liu, S. (2016). miR-21 and miR-155 promote non-small cell lung cancer progression by downregulating *SOCS1*, *SOCS6*, and *PTEN*. Oncotarget *7*, 84508–84519.
67. Peng, J., Liu, H., and Liu, C. (2017). miR-155 promotes uveal melanoma cell proliferation and invasion by regulating NDFIP1 expression. Technol. Cancer Res. Treat. *16*, 1160–1167.
68. Ling, J.W., Lu, P.R., Zhang, Y.B., Jiang, S., and Zhang, Z.C. (2017). miR-367 promotes uveal melanoma cell proliferation and migration by regulating PTEN. Genet. Mol. Res. *16*, gmr16039067.
69. Mao, X.H., Chen, M., Wang, Y., Cui, P.G., Liu, S.B., and Xu, Z.Y. (2017). MicroRNA-21 regulates the ERK/NF-κB signaling pathway to affect the proliferation, migration, and apoptosis of human melanoma A375 cells by targeting SPRY1, PDCD4, and PTEN. Mol. Carcinog. *56*, 886–894.
70. Bhattacharya, A., Schmitz, U., Raatz, Y., Schönherr, M., Kottek, T., Schauer, M., Franz, S., Saalbach, A., Anderegg, U., Wolkenhauer, O., et al. (2015). miR-638 promotes melanoma metastasis and protects melanoma cells from apoptosis and autophagy. Oncotarget *6*, 2966–2980.
71. Vergani, E., Di Guardo, L., Dugo, M., Rigoletto, S., Tragni, G., Ruggeri, R., Perrone, F., Tamborini, E., Gloghini, A., Arienti, F., et al. (2016). Overcoming melanoma resistance to vemurafenib by targeting CCL2-induced miR-34a, miR-100 and miR-125b. Oncotarget *7*, 4428–4441.
72. Liu, N., Sun, Q., Chen, J., Li, J., Zeng, Y., Zhai, S., Li, P., Wang, B., and Wang, X. (2012). MicroRNA-9 suppresses uveal melanoma cell migration and invasion through the NF-κB1 pathway. Oncol. Rep. *28*, 961–968.
73. Schultz, J., Lorenz, P., Gross, G., Ibrahim, S., and Kunz, M. (2008). MicroRNA let-7b targets important cell cycle molecules in malignant melanoma cells and interferes with anchorage-independent growth. Cell Res. *18*, 549–557.
74. Yan, D., Zhou, X., Chen, X., Hu, D.N., Dong, X.D., Wang, J., Lu, F., Tu, L., and Qu, J. (2009). MicroRNA-34a inhibits uveal melanoma cell proliferation and migration through downregulation of c-Met. Invest. Ophthalmol. Vis. Sci. *50*, 1559–1565.
75. Liu, S., Tetzlaff, M.T., Cui, R., and Xu, X. (2012). miR-200c inhibits melanoma progression and drug resistance through down-regulation of BMI-1. Am. J. Pathol. *181*, 1823–1835.
76. Liu, S., Tetzlaff, M.T., Wang, T., Yang, R., Xie, L., Zhang, G., Krepler, C., Xiao, M., Beqiri, M., Xu, W., et al. (2015). miR-200c/Bmi1 axis and epithelial-mesenchymal transition contribute to acquired resistance to BRAF inhibitor treatment. Pigment Cell Melanoma Res. *28*, 431–441.
77. Pan, B.T., and Johnstone, R.M. (1983). Fate of the transferrin receptor during maturation of sheep reticulocytes in vitro: Selective externalization of the receptor. Cell *33*, 967–978.
78. Karin-Kujundzic, V., Sola, I.M., Predavec, N., Potkonjak, A., Somen, E., Mioc, P., Serman, A., Vranic, S., and Serman, L. (2019). Novel epigenetic biomarkers in pregnancy-related disorders and cancers. Cells *8*, 1459.
79. Jella, K.K., Nasti, T.H., Li, Z., Malla, S.R., Buchwald, Z.S., and Khan, M.K. (2018). Exosomes, their biogenesis and role in inter-cellular communication, tumor microenvironment and cancer immunotherapy. Vaccines (Basel) *6*, 69.
80. Tucci, M., Passarelli, A., Mannavola, F., Stucci, L.S., Ascierto, P.A., Capone, M., Madonna, G., Lopalco, P., and Silvestris, F. (2017). Serum exosomes as predictors of clinical response to ipilimumab in metastatic melanoma. OncoImmunology *7*, e1387706.
81. Qian, Z., Shen, Q., Yang, X., Qiu, Y., and Zhang, W. (2015). the role of extracellular vesicles: An epigenetic view of the cancer microenvironment. BioMed Res. Int. *2015*, 649161.
82. Peinado, H., Alečković, M., Lavotshkin, S., Matei, I., Costa-Silva, B., Moreno-Bueno, G., Hergueta-Redondo, M., Williams, C., García-Santos, G., Ghajar, C., et al. (2012). Melanoma exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype through MET. Nat. Med. *18*, 883–891.
83. Rappa, G., Mercapide, J., Anzanello, F., Pope, R.M., and Lorico, A. (2013). Biochemical and biological characterization of exosomes containing prominin-1/CD133. Mol. Cancer *12*, 62.
84. Xiao, D., Ohlendorf, J., Chen, Y., Taylor, D.D., Rai, S.N., Waigel, S., Zacharias, W., Hao, H., and McMasters, K.M. (2012). Identifying mRNA, microRNA and protein profiles of melanoma exosomes. PLoS ONE *7*, e46874.
85. Wang, T., Gilkes, D.M., Takano, N., Xiang, L., Luo, W., Bishop, C.J., Chaturvedi, P., Green, J.J., and Semenza, G.L. (2014). Hypoxia-inducible factors and RAB22A mediate formation of microvesicles that stimulate breast cancer invasion and metastasis. Proc. Natl. Acad. Sci. USA *111*, E3234–E3242.
86. Dror, S., Sander, L., Schwartz, H., Sheinboim, D., Barzilai, A., Dishon, Y., Apcher, S., Golan, T., Greenberger, S., Barshack, I., et al. (2016). Melanoma miRNA trafficking controls tumour primary niche formation. Nat. Cell Biol. *18*, 1006–1017.
87. Kawakami, Y., Sumimoto, H., Fujita, T., and Matsuzaki, Y. (2005). Immunological detection of altered signaling molecules involved in melanoma development. Cancer Metastasis Rev. *24*, 357–366.
88. Postow, M.A., Chesney, J., Pavlick, A.C., Robert, C., Grossmann, K., McDermott, D., Linette, G.P., Meyer, N., Giguere, J.K., Agarwala, S.S., et al. (2015). Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N. Engl. J. Med. *372*, 2006–2017.
89. Larkin, J., Chiarion-Sileni, V., Gonzalez, R., Grob, J.J., Cowey, C.L., Lao, C.D., Schadendorf, D., Dummer, R., Smylie, M., Rutkowski, P., et al. (2015). Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N. Engl. J. Med. *373*, 23–34.
90. Robert, C., Long, G.V., Brady, B., Dutriaux, C., Maio, M., Mortier, L., Hassel, J.C., Rutkowski, P., McNeil, C., Kalinka-Warzocha, E., et al. (2015). Nivolumab in previously untreated melanoma without *BRAF* mutation. N. Engl. J. Med. *372*, 320–330.
91. Gaziel-Sovran, A., Segura, M.F., Di Micco, R., Collins, M.K., Hanniford, D., Vega-Saenz de Miera, E., Rakus, J.F., Dankert, J.F., Shang, S., Kerbel, R.S., et al. (2011). miR-30b/30d regulation of GalNAc transferases enhances invasion and immunosuppression during metastasis. Cancer Cell *20*, 104–118.
92. Wang, P., Gu, Y., Zhang, Q., Han, Y., Hou, J., Lin, L., Wu, C., Bao, Y., Su, X., Jiang, M., et al. (2012). Identification of resting and type I IFN-activated human NK cell miRNomes reveals microRNA-378 and microRNA-30e as negative regulators of NK cell cytotoxicity. J. Immunol. *189*, 211–221.
93. Trotta, R., Chen, L., Ciarlariello, D., Josyula, S., Mao, C., Costinean, S., Yu, L., Butchar, J.P., Tridandapani, S., Croce, C.M., and Caligiuri, M.A. (2012). miR-155 regulates IFN-γ production in natural killer cells. Blood *119*, 3478–3485.

94. Arts, N., Cané, S., Hennequart, M., Lamy, J., Bommer, G., Van den Eynde, B., and De Plaen, E. (2015). MicroRNA-155, induced by interleukin-1ß, represses the expression of microphthalmia-associated transcription factor (MITF-M) in melanoma cells. PLoS ONE *10*, e0122517.

95. Taganov, K.D., Boldin, M.P., Chang, K.J., and Baltimore, D. (2006). NF-κB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. Proc. Natl. Acad. Sci. USA *103*, 12481–12486.

96. Lee, H.M., Kim, T.S., and Jo, E.K. (2016). miR-146 and miR-125 in the regulation of innate immunity and inflammation. BMB Rep. *49*, 311–318.

97. Bustos, M.A., Ono, S., Marzese, D.M., Oyama, T., Iida, Y., Cheung, G., Nelson, N., Hsu, S.C., Yu, Q., and Hoon, D.S.B. (2017). miR-200a regulates CDK4/6 inhibitor effect by targeting CDK6 in metastatic melanoma. J. Invest. Dermatol. *137*, 1955–1964.

98. Segura, M.F., Greenwald, H.S., Hanniford, D., Osman, I., and Hernando, E. (2012). MicroRNA and cutaneous melanoma: from discovery to prognosis and therapy. Carcinogenesis *33*, 1823–1832.

99. Tong, A.W., and Nemunaitis, J. (2008). Modulation of miRNA activity in human cancer: A new paradigm for cancer gene therapy? Cancer Gene Ther. *15*, 341–355.

100. Huynh, C., Segura, M.F., Gaziel-Sovran, A., Menendez, S., Darvishian, F., Chiriboga, L., Levin, B., Meruelo, D., Osman, I., Zavadil, J., et al. (2011). Efficient in vivo microRNA targeting of liver metastasis. Oncogene *30*, 1481–1488.

101. Wang, H.F., Chen, H., Ma, M.W., Wang, J.A., Tang, T.T., Ni, L.S., Yu, J.L., Li, Y.Z., and Bai, B.X. (2013). miR-573 regulates melanoma progression by targeting the melanoma cell adhesion molecule. Oncol. Rep. *30*, 520–526.

102. Yoon, J.H., Abdelmohsen, K., and Gorospe, M. (2013). Posttranscriptional gene regulation by long noncoding RNA. J. Mol. Biol. *425*, 3723–3730.

103. Yu, Y., Yarrington, R.M., Chuong, E.B., Elde, N.C., and Stillman, D.J. (2016). Disruption of promoter memory by synthesis of a long noncoding RNA. Proc. Natl. Acad. Sci. USA *113*, 9575–9580.

104. Ntziachristos, P., Abdel-Wahab, O., and Aifantis, I. (2016). Emerging concepts of epigenetic dysregulation in hematological malignancies. Nat. Immunol. *17*, 1016–1024.

105. Clark, M.B., Amaral, P.P., Schlesinger, F.J., Dinger, M.E., Taft, R.J., Rinn, J.L., Ponting, C.P., Stadler, P.F., Morris, K.V., Morillon, A., et al. (2011). The reality of pervasive transcription. PLoS Biol. *9*, e1000625.

106. Huarte, M. (2015). The emerging role of lncRNAs in cancer. Nat. Med. *21*, 1253–1261.

107. Li, R., Zhang, L., Jia, L., Duan, Y., Li, Y., Bao, L., and Sha, N. (2014). Long non-coding RNA BANCR promotes proliferation in malignant melanoma by regulating MAPK pathway activation. PLoS ONE *9*, e100893.

108. Tang, L., Zhang, W., Su, B., and Yu, B. (2013). Long noncoding RNA HOTAIR is associated with motility, invasion, and metastatic potential of metastatic melanoma. BioMed Res. Int. *2013*, 251098.

109. Pasmant, E., Laurendeau, I., Héron, D., Vidaud, M., Vidaud, D., and Bièche, I. (2007). Characterization of a germ-line deletion, including the entire *INK4/ARF* locus, in a melanoma-neural system tumor family: identification of *ANRIL*, an antisense noncoding RNA whose expression coclusters with *ARF*. Cancer Res. *67*, 3963–3969.

110. Tian, Y., Zhang, X., Hao, Y., Fang, Z., and He, Y. (2014). Potential roles of abnormally expressed long noncoding RNA UCA1 and Malat-1 in metastasis of melanoma. Melanoma Res. *24*, 335–341.

111. Leucci, E., Vendramin, R., Spinazzi, M., Laurette, P., Fiers, M., Wouters, J., Radaelli, E., Eyckerman, S., Leonelli, C., Vanderheyden, K., et al. (2016). Melanoma addiction to the long non-coding RNA SAMMSON. Nature *531*, 518–522.

112. Wang, B.J., Ding, H.W., and Ma, G.A. (2018). Long noncoding RNA PVT1 promotes melanoma progression via endogenous sponging miR-26b. Oncol. Res. *26*, 675–681.

113. Schmidt, K., Joyce, C.E., Buquicchio, F., Brown, A., Ritz, J., Distel, R.J., Yoon, C.H., and Novina, C.D. (2016). The lncRNA *SLNCR1* mediates melanoma invasion through a conserved *SRA1*-like region. Cell Rep. *15*, 2025–2037.

114. Wei, Y., Sun, Q., Zhao, L., Wu, J., Chen, X., Wang, Y., Zang, W., and Zhao, G. (2016). lncRNA UCA1-miR-507-FOXM1 axis is involved in cell proliferation, invasion and G0/G1 cell cycle arrest in melanoma. Med. Oncol. *33*, 88.

115. Guo, J.R., Yin, L., Chen, Y.Q., Jin, X.J., Zhou, X., Zhu, N.N., Liu, X.Q., Wei, H.W., and Duan, L.S. (2018). Autologous blood transfusion augments impaired wound healing in diabetic mice by enhancing lncRNA H19 expression via the HIF-1α signaling pathway. Cell Commun. Signal. *16*, 84.

116. Lu, Q., Zhao, N., Zha, G., Wang, H., Tong, Q., and Xin, S. (2017). lncRNA HOXA11-AS exerts oncogenic functions by repressing p21 and miR-124 in uveal melanoma. DNA Cell Biol. *36*, 837–844.

117. Read, J., Wadt, K.A., and Hayward, N.K. (2016). Melanoma genetics. J. Med. Genet. *53*, 1–14.

118. Sarkar, D., Leung, E.Y., Baguley, B.C., Finlay, G.J., and Askarian-Amiri, M.E. (2015). Epigenetic regulation in human melanoma: past and future. Epigenetics *10*, 103–121.

119. Holdt, L.M., and Teupser, D. (2018). Long noncoding RNA *ANRIL*: lnc-ing genetic variation at the chromosome 9p21 locus to molecular mechanisms of atherosclerosis. Front. Cardiovasc. Med. *5*, 145.

120. Nie, F.Q., Sun, M., Yang, J.S., Xie, M., Xu, T.P., Xia, R., Liu, Y.W., Liu, X.H., Zhang, E.B., Lu, K.H., and Shu, Y.Q. (2015). Long noncoding RNA ANRIL promotes non-small cell lung cancer cell proliferation and inhibits apoptosis by silencing KLF2 and P21 expression. Mol. Cancer Ther. *14*, 268–277.

121. Sun, Y., Zheng, Z.P., Li, H., Zhang, H.Q., and Ma, F.Q. (2016). ANRIL is associated with the survival rate of patients with colorectal cancer, and affects cell migration and invasion in vitro. Mol. Med. Rep. *14*, 1714–1720.

122. Zheng, X., Tang, H., Zhao, X., Sun, Y., Jiang, Y., and Liu, Y. (2017). Long non-coding RNA FTH1P3 facilitates uveal melanoma cell growth and invasion through miR-224-5p. PLoS ONE *12*, e0184746.

123. Zhang, R., Xia, Y., Wang, Z., Zheng, J., Chen, Y., Li, X., Wang, Y., and Ming, H. (2017). Serum long non coding RNA MALAT-1 protected by exosomes is up-regulated and promotes cell proliferation and migration in non-small cell lung cancer. Biochem. Biophys. Res. Commun. *490*, 406–414.

124. Luo, P., Liu, X.F., Wang, Y.C., Li, N.D., Liao, S.J., Yu, M.X., Liang, C.Z., and Tu, J.C. (2017). Prognostic value of abnormally expressed lncRNAs in ovarian carcinoma: a systematic review and meta-analysis. Oncotarget *8*, 23927–23936.

125. Xie, M., Nie, F.Q., Sun, M., Xia, R., Liu, Y.W., Zhou, P., De, W., and Liu, X.H. (2015). Decreased long noncoding RNA SPRY4-IT1 contributing to gastric cancer cell metastasis partly via affecting epithelial-mesenchymal transition. J. Transl. Med. *13*, 250.

126. Liu, H., Lv, Z., and Guo, E. (2015). Knockdown of long noncoding RNA SPRY4-IT1 suppresses glioma cell proliferation, metastasis and epithelial-mesenchymal transition. Int. J. Clin. Exp. Pathol. *8*, 9140–9146.

127. Mouraviev, V., Lee, B., Patel, V., Albala, D., Johansen, T.E., Partin, A., Ross, A., and Perera, R.J. (2016). Clinical prospects of long noncoding RNAs as novel biomarkers and therapeutic targets in prostate cancer. Prostate Cancer Prostatic Dis. *19*, 14–20.

128. Xie, H.W., Wu, Q.Q., Zhu, B., Chen, F.J., Ji, L., Li, S.Q., Wang, C.M., Tong, Y.S., Tuo, L., Wu, M., et al. (2014). Long noncoding RNA SPRY4-IT1 is upregulated in esophageal squamous cell carcinoma and associated with poor prognosis. Tumour Biol. *35*, 7743–7754.

129. Mazar, J., Zhao, W., Khalil, A.M., Lee, B., Shelley, J., Govindarajan, S.S., Yamamoto, F., Ratnam, M., Aftab, M.N., Collins, S., et al. (2014). The functional characterization of long noncoding RNA SPRY4-IT1 in human melanoma cells. Oncotarget *5*, 8959–8969.

130. Wang, Z., Wang, X., Zhou, H., Dan, X., Jiang, L., and Wu, Y. (2018). Long non-coding RNA CASC2 inhibits tumorigenesis via the miR-181a/*PLXNC1* axis in melanoma. Acta Biochim. Biophys. Sin. (Shanghai) *50*, 263–272.

131. Ard, R., Allshire, R.C., and Marquardt, S. (2017). Emerging properties and functional consequences of noncoding transcription. Genetics *207*, 357–367.

132. Li, C.H., and Chen, Y. (2013). Targeting long non-coding RNAs in cancers: Progress and prospects. Int. J. Biochem. Cell Biol. *45*, 1895–1910.

133. Wu, C.F., Tan, G.H., Ma, C.C., and Li, L. (2013). The non-coding RNA Llme23 drives the malignant property of human melanoma cells. J. Genet. Genomics *40*, 179–188.

134. Sanger, H.L., Klotz, G., Riesner, D., Gross, H.J., and Kleinschmidt, A.K. (1976). Viroids are single-stranded covalently closed circular RNA molecules existing as highly base-paired rod-like structures. Proc. Natl. Acad. Sci. USA *73*, 3852–3856.

135. Salzman, J., Gawad, C., Wang, P.L., Lacayo, N., and Brown, P.O. (2012). Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. PLoS ONE *7*, e30733.

136. Shang, Q., Li, Y., Wang, H., Ge, S., and Jia, R. (2019). Altered expression profile of circular RNAs in conjunctival melanoma. Epigenomics *11*, 787–804.

137. Yang, X., Li, Y., Liu, Y., Xu, X., Wang, Y., Yan, Y., Zhou, W., Yang, J., and Wei, W. (2018). Novel circular RNA expression profile of uveal melanoma revealed by microarray. Chin. J. Cancer Res. *30*, 656–668.

138. Chen, Z., Chen, J., Wa, Q., He, M., Wang, X., Zhou, J., and Cen, Y. (2020). Knockdown of circ_0084043 suppresses the development of human melanoma cells through miR-429/tribbles homolog 2 axis and Wnt/β-catenin pathway. Life Sci. *243*, 117323.

139. Hanniford, D., Ulloa-Morales, A., Karz, A., Berzoti-Coelho, M.G., Moubarak, R.S., Sánchez-Sendra, B., Kloetgen, A., Davalos, V., Imig, J., Wu, P., et al. (2020). Epigenetic silencing of *CDR1as* drives IGF2BP3-mediated melanoma invasion and metastasis. Cancer Cell *37*, 55–70.e15.

140. Chen, Z., Kang, K., Chen, S., Wang, S., Zhang, J., Zhang, X.Y., and Chen, Z. (2020). Retraction. Eur. Rev. Med. Pharmacol. Sci. *24*, 8630.

141. Jin, C., Dong, D., Yang, Z., Xia, R., Tao, S., and Piao, M. (2020). circMYC regulates glycolysis and cell proliferation in melanoma. Cell Biochem. Biophys. *78*, 77–88.

142. Tian, S., Han, G., Lu, L., and Meng, X. (2020). circ-FOXM1 contributes to cell proliferation, invasion, and glycolysis and represses apoptosis in melanoma by regulating miR-143-3p/FLOT2 axis. World J. Surg. Oncol. *18*, 56.

143. Lin, Q., Jiang, H., and Lin, D. (2021). Circular RNA ITCH downregulates GLUT1 and suppresses glucose uptake in melanoma to inhibit cancer cell proliferation. J. Dermatolog. Treat. *32*, 231–235.

144. Zou, Y., Wang, S.S., Wang, J., Su, H.L., and Xu, J.H. (2019). circRNA_0016418 expedites the progression of human skin melanoma via miR-625/YY1 axis. Eur. Rev. Med. Pharmacol. Sci. *23*, 10918–10930.

145. Bian, D., Wu, Y., and Song, G. (2018). Novel circular RNA, hsa_circ_0025039 promotes cell growth, invasion and glucose metabolism in malignant melanoma via the miR-198/CDK4 axis. Biomed. Pharmacother. *108*, 165–176.

146. Jeck, W.R., and Sharpless, N.E. (2014). Detecting and characterizing circular RNAs. Nat. Biotechnol. *32*, 453–461.

147. Li, Z., Huang, C., Bao, C., Chen, L., Lin, M., Wang, X., Zhong, G., Yu, B., Hu, W., Dai, L., et al. (2015). Exon-intron circular RNAs regulate transcription in the nucleus. Nat. Struct. Mol. Biol. *22*, 256–264.

148. Werfel, S., Nothjunge, S., Schwarzmayr, T., Strom, T.M., Meitinger, T., and Engelhardt, S. (2016). Characterization of circular RNAs in human, mouse and rat hearts. J. Mol. Cell. Cardiol. *98*, 103–107.

149. Chen, W., and Schuman, E. (2016). Circular RNAs in brain and other tissues: A functional enigma. Trends Neurosci. *39*, 597–604.

150. Dong, R., Ma, X.K., Chen, L.L., and Yang, L. (2017). Increased complexity of circRNA expression during species evolution. RNA Biol. *14*, 1064–1074.

151. Salmena, L., Poliseno, L., Tay, Y., Kats, L., and Pandolfi, P.P. (2011). A ceRNA hypothesis: The Rosetta Stone of a hidden RNA language? Cell *146*, 353–358.

152. Jeck, W.R., Sorrentino, J.A., Wang, K., Slevin, M.K., Burd, C.E., Liu, J., Marzluff, W.F., and Sharpless, N.E. (2013). Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA *19*, 141–157.

153. Guo, J.U., Agarwal, V., Guo, H., and Bartel, D.P. (2014). Expanded identification and characterization of mammalian circular RNAs. Genome Biol. *15*, 409.

154. Legnini, I., Di Timoteo, G., Rossi, F., Morlando, M., Briganti, F., Sthandier, O., Fatica, A., Santini, T., Andronache, A., Wade, M., et al. (2017). circ-ZNF609 is a circular RNA that can be translated and functions in myogenesis. Mol. Cell *66*, 22–37.e9.

155. Qu, S., Yang, X., Li, X., Wang, J., Gao, Y., Shang, R., Sun, W., Dou, K., and Li, H. (2015). Circular RNA: A new star of noncoding RNAs. Cancer Lett. *365*, 141–148.

156. Ju, H., Zhang, L., Mao, L., Liu, S., Xia, W., Hu, J., Ruan, M., and Ren, G. (2018). Altered expression pattern of circular RNAs in metastatic oral mucosal melanoma. Am. J. Cancer Res. *8*, 1788–1800.

157. Sun, X., Li, J., Sun, Y., Zhang, Y., Dong, L., Shen, C., Yang, L., Yang, M., Li, Y., Shen, G., et al. (2016). miR-7 reverses the resistance to BRAFi in melanoma by targeting EGFR/IGF-1R/CRAF and inhibiting the MAPK and PI3K/AKT signaling pathways. Oncotarget *7*, 53558–53570.

158. Mishra, P.J., Mishra, P.J., and Merlino, G. (2016). Integrated genomics identifies miR-32/MCL-1 pathway as a critical driver of melanomagenesis: Implications for miR-replacement and combination therapy. PLoS ONE *11*, e0165102.

159. Fattore, L., Mancini, R., Acunzo, M., Romano, G., Laganà, A., Pisanu, M.E., Malpicci, D., Madonna, G., Mallardo, D., Capone, M., et al. (2016). miR-579-3p controls melanoma progression and resistance to target therapy. Proc. Natl. Acad. Sci. USA *113*, E5005–E5013.

160. Li, Y., Zhang, J., Liu, Y., Zhang, B., Zhong, F., Wang, S., and Fang, Z. (2018). miR-30a-5p confers cisplatin resistance by regulating IGF1R expression in melanoma cells. BMC Cancer *18*, 404.

161. Tian, R., Liu, T., Qiao, L., Gao, M., and Li, J. (2015). Decreased serum microRNA-206 level predicts unfavorable prognosis in patients with melanoma. Int. J. Clin. Exp. Pathol. *8*, 3097–3103.

162. Li, P., He, Q.Y., Luo, C.Q., and Qian, L.Y. (2014). Circulating miR-221 expression level and prognosis of cutaneous malignant melanoma. Med. Sci. Monit. *20*, 2472–2477.

163. Alegre, E., Sanmamed, M.F., Rodriguez, C., Carranza, O., Martín-Algarra, S., and González, A. (2014). Study of circulating microRNA-125b levels in serum exosomes in advanced melanoma. Arch. Pathol. Lab. Med. *138*, 828–832.

164. Piipponen, M., Nissinen, L., Farshchian, M., Riihilä, P., Kivisaari, A., Kallajoki, M., Peltonen, J., Peltonen, S., and Kähäri, V.M. (2016). Long noncoding RNA PICSAR promotes growth of cutaneous squamous cell carcinoma by regulating ERK1/2 activity. J. Invest. Dermatol. *136*, 1701–1710.

165. Luan, W., Li, R., Liu, L., Ni, X., Shi, Y., Xia, Y., Wang, J., Lu, F., and Xu, B. (2017). Long non-coding RNA HOTAIR acts as a competing endogenous RNA to promote malignant melanoma progression by sponging miR-152-3p. Oncotarget *8*, 85401–85414.

166. Li, X., Chen, B., Chi, D., Zhang, Y., and Jiang, W. (2019). lncRNA CASC9 regulates cell migration and invasion in hemangioma endothelial cells by targeting miR-125a-3p/Nrg1. OncoTargets Ther. *12*, 423–432.

167. Sousa, J.F., Torrieri, R., Silva, R.R., Pereira, C.G., Valente, V., Torrieri, E., Peronni, K.C., Martins, W., Muto, N., Francisco, G., et al. (2010). Novel primate-specific genes, RMEL 1, 2 and 3, with highly restricted expression in melanoma, assessed by new data mining tool. PLoS ONE *5*, e13510.

168. Leucci, E., Coe, E.A., Marine, J.C., and Vance, K.W. (2016). The emerging role of long non-coding RNAs in cutaneous melanoma. Pigment Cell Melanoma Res. *29*, 619–626.

169. Sun, Y., Cheng, H., Wang, G., Yu, G., Zhang, D., Wang, Y., Fan, W., and Yang, W. (2017). Deregulation of miR-183 promotes melanoma development via lncRNA MALAT1 regulation and ITGB1 signal activation. Oncotarget *8*, 3509–3518.

170. Luan, W., Shi, Y., Zhou, Z., Xia, Y., and Wang, J. (2018). circRNA_0084043 promote malignant melanoma progression via miR-153-3p/Snail axis. Biochem. Biophys. Res. Commun. *502*, 22–29.

171. Wei, C.Y., Zhu, M.X., Lu, N.H., Liu, J.Q., Yang, Y.W., Zhang, Y., Shi, Y.D., Feng, Z.H., Li, J.X., Qi, F.Z., and Gu, J.Y. (2020). Circular RNA circ_0020710 drives tumor progression and immune evasion by regulating the miR-370-3p/CXCL12 axis in melanoma. Mol. Cancer *19*, 84.

172. Chen, J., Zhou, X., Yang, J., Sun, Q., Liu, Y., Li, N., Zhang, Z., and Xu, H. (2020). circ-GLI1 promotes metastasis in melanoma through interacting with p70S6K2 to activate Hedgehog/GLI1 and Wnt/β-catenin pathways and upregulate Cyr61. Cell Death Dis. *11*, 596.

173. Qian, P., Linbo, L., Xiaomei, Z., and Hui, P. (2020). circ_0002770, acting as a competitive endogenous RNA, promotes proliferation and invasion by targeting miR-331-3p in melanoma. Cell Death Dis. *11*, 264.