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Review

The role of microRNAs and long non-coding RNAs in the pathology, diagnosis, and management of melanoma

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ABSTRACT

Melanoma is frequently lethal and its global incidence is steadily increasing. Despite the rapid development of different modes of targeted treatment, durable clinical responses remain elusive. A complete understanding of the molecular mechanisms that drive melanomagenesis is required, both genetic and epigenetic, in order to improve prevention, diagnosis, and treatment. There is increased appreciation of the role of microRNAs (miRNAs) in melanoma biology, including in proliferation, cell cycle, migration, invasion, and immune evasion. Data are also emerging on the role of long non-coding RNAs (lncRNAs), such as SPRY4-IT1, BANCR, and HOTAIR, in melanomagenesis. Here we review the data on the miRNAs and lncRNAs implicated in melanoma biology. An overview of these studies will be useful for providing insights into mechanisms of melanoma development and the miRNAs and lncRNAs that might be useful biomarkers or future therapeutic targets.

Introduction

Melanoma is the leading cause of skin cancer deaths in the United States [1]. Melanoma survival rates are good when the disease is detected early; precise diagnostic tests for early melanoma detection would therefore be useful, and innovative therapies to cure advanced melanomas are needed. The underlying molecular biology of melanomas is complex and involves interactions between networks of genes, signaling pathways, and gene-regulatory mechanisms, and a better understanding of these underlying molecular mechanisms is essential for translational research. In addition, the histopathologic interpretation of cutaneous melanoma remains one of the most frustrating and difficult diagnostic areas in dermatopathology, and histopathologists would benefit from sensitive and specific diagnostic biomarkers. A number of protein-coding genes [2] have been identified as potential diagnostic and prognostic biomarkers [3–9], several of which exhibit distinct expression profiles between the spectrum of malignant melanomas and their benign forms [2]. In addition, non-protein-coding RNAs (microRNAs and long non-coding RNAs (lncRNAs))[1] are emerging as early prognostic markers and therapeutic targets in a variety of diseases, and microRNAs (miRNAs) is particular have gained increasing attention due to their potential roles in tumorigenesis [10–14], not least in melanoma [15–19]. miRNAs are thought to influence cancer development by regulating transcription and translation of tumor suppressor genes and oncogenes [20–26]. Several genome-wide expression studies have implicated a number of miRNAs and lncRNAs that are potentially important regulators of melanoma development [9,19,27,28].

Melanocytes are skin cells that originate from neural crest cells and have the ability to produce the pigment melanin [1]. Melanocyte differentiation occurs via a series of steps, ultimately resulting in lineage specification of melanoblasts and transportation of mature melanosomes to keratinocytes [29,30]. Melanocytes are

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[1] *Abbreviations used:* lncRNAs, long non-coding RNAs; MITF, microphthalmia transcription factor; *TRPM1*, transient receptor potential cation channel subfamily M member 1; *RUNX2*, Runt-related transcription factor 2; *IGF2R*, insulin-like growth factor 2 receptor; *TGFBR2*, TGF-beta receptor 2; *NFAT5*, nuclear factor of activated T cells 5; NKG2D, natural killer cell immunoreceptor; bFGF, basic fibroblast growth factor; BMP-4, bone morphogenetic protein 4; CTLs, cytotoxic T lymphocytes; CDKs, cyclin-dependent kinases; kif5b, kinesin superfamily protein 5b; eIF4E, eukaryotic translation initiation factor 4; GSK3α, glycogen synthase kinase-3α; FSCN1, fascin actin-bundling protein 1; FFPE, formalin-fixed paraffin-embedded; SODD, silence of death domain; PSF, protein-associated splicing factor; SNPs, single nucleotide polymorphisms.

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characterized by the expression of melanocyte-specific proteins, including tyrosinase, tyrosinase-related protein 1 and 2, melanosomal matrix proteins (Pmel17, MART-1), and microphthalmia transcription factor (MITF) [1]. Genes such as *MITF*, [31] *PAX3*, *SOX10* [32–34], members of the Wnt and Notch signaling pathways [35–37], *KIT*, and cyclins [38] all play an important role in the development and regulation of melanocytes.

Melanogenesis is a stepwise metamorphic process in which normal melanocytes in the epidermis gradually transform into the vertical growth phase characteristic of malignant melanomas [39]. Several factors influence the transformation of melanocytes into melanomas, such as UV exposure [40], melanocyte integrity [41], melanocyte homeostatic mechanisms [42], and neural crest invasion and differentiation [43,44]. In addition to the many protein-coding genes that regulate cancer development, many non-coding genes have also been shown to play important roles in cancer prognosis, diagnosis, and therapy. These include the small RNAs, in particular miRNAs and lncRNAs. Due to wide spread increase and mortality of melanoma globally, it is important to discuss ways and means for the insight mechanism of transformation of melanocytes into melanoma. On the basis of basic information, many methods have been proposed for the prognosis and treatment of melanoma. In this review, we have discussed the possible role of miRNAs in the pathology, diagnosis, and treatment of melanoma. Although role of lncRNAs in melanoma is not fully established, still lncRNAs were given due consideration for their involvement in melanoma.

miRNAs in melanocytes and melanoma biology

miRNAs are small, non-coding RNAs that play a physiological role in the post-transcriptional fine-tuning of the expression of up to 60% of mammalian protein-coding genes [45,46]. The aberrant expression and function of miRNAs has been linked to the development and progression of many human diseases, Fig. 1 including various cancers [10–14], not least melanoma [15–19]. As a result of systematic experimental screens for miRNAs involved in the development and progression of melanoma, several groups have identified miR-211 as the miRNA most differentially expressed between normal melanocytes and non-pigmented melanoma cell lines and primary melanomas from patients [47–52]. Ectopic expression of *miR-211* in melanoma cell lines results in significant inhibition of growth and invasion compared to parental cells, suggesting that *miR-211* normally functions as a tumor suppressor in melanocytes. This hypothesis is supported by the finding that *miR-211* is encoded by a region in the sixth intron of *TRPM1* (transient receptor potential cation channel subfamily M member 1), a candidate suppressor of melanoma metastasis [47,48]. Moreover, we have also reported that the expression of *TRPM1* and *miR-211* are controlled by MITF, a master regulator of melanocyte development and function. It is therefore possible that the tumor suppressor activities of MITF and/or TRPM1 may be mediated, at least in part, by *miR-211*. Recently, several *miR-211* target genes have been identified, including Runt-related transcription factor 2 (*RUNX2)*, insulin-like growth factor 2 receptor (*IGF2R),* TGF-beta receptor 2 (*TGFBR2)*, the POU domain-containing transcription factor *BRN2,* and nuclear factor of activated T cells 5 (*NFAT5)* [48,53].

miR-211 may also directly regulate melanocyte pigmentation and invasion, since it is highly expressed in melanocytes and pigmented melanomas but not in non-pigmented melanomas (Mazar et al., personal communication). Melanomas with greatly reduced *miR-211* expression are highly invasive [47,54,55]. Conversely, melanoma cells that highly express *miR-211* have reduced invasive potential [52], independent of expression of melastatin that was able to block formation of tumor nodules [56]. Together, these findings provide strong evidence that *miR-211* plays a critical role in melanoma invasiveness and progression.

In an attempt to explain the mechanistic basis for these findings, a melanoma-specific metastasis gene network was scrutinized for overlaps between metastatic genes and miR-211 target genes [54]. Six genes overlapped: *IGF2R*, *NFAT5*, *TGFBR2*, *FBXW7*, *ANGPT1*, *IGFBPS* and *VHL*. Functional validation showed that knockdown of 'central node genes' had the same effect on melanoma cell invasion as up-regulation of *miR-211*. Of these, *TGFB* had previously been linked to melanoma progression via promotion of tissue and blood vessel invasion. More recently, Bell et al. [52] tried to establish which relationships between transcription factors and miRNAs were important for melanoma proliferation and invasion using gene expression profiling of normal and melanoma cells. Several miRNAs known to regulate proliferation and invasion were identified, including *miR-211*. A new *miR-211* target, *NUAK1*, was also identified, which was shown to play a role in melanoma cell adhesion with downregulation of *miR-211* upregulating NUAK1 and promoting adhesion, and vice versa.

miR-196a has also been shown to act as a tumor suppressor miRNA in melanoma [57]. Using a high-throughput miRNA expression profiling approach in cell lines and tissue samples, *miR-196a* expression was found to be significantly reduced in malignant lesions. Over-expression of *miR-196a* significantly reduced the invasive capacity of melanoma cells, and HOX-C8, cadherin-11, calponin-1, and osteopontin were identified asmiR-196a targets. These authors then went on to show that *miR-196a* downregulation led to upregulation of HOX-B7 and consequent stimulation of basic fibroblast growth factor (bFGF) signaling, with resulting ETS-1 transcription factor and bone morphogenetic protein 4 (BMP-4) expression, which is known play a role in melanoma progression [58]. Using similar methodology, Chen et al. showed that *miR-193b* also acts as a tumor suppressor via cyclin D1, and it was the most downregulated of 31 differentially expressed miRNAs in malignant tissue samples.

It has been shown that miRNA regulatory effect on their targets is directly correlated to mRNA decay [59,60]. mRNA decay rates in animal cells changes rapidly and with half-lives varying from minutes to days [61]. For example, for mRNAs stability in mouse embryonic stem cells the median is around 7 h, whereas some genes, including *Foxa2*, *Hes5* and *Trib1*, have half-lives under an hour [62]. In a recent study, Larsson et al., [59] reported that the short-lived transcripts are more difficult to perturb using microRNAs. Therefore, it is important to take this (mRNA stability/decay rate) in to account when designing a miRNA perturbation study.

The role of miRNAs in the immune response

Hypoxia influences the microenvironment of solid tumors, including in melanoma. One effect of hypoxia in melanoma is that it is thought to facilitate escape from immune control and promote cancer via downregulation of antigens and proteins that are necessary for an effective immune response [134,135].

Hypoxia is known to stimulate expression of several miRNAs. miR-210 is regulated during HIF1-α-dependent hypoxia in non-small cell lung cancer (IGR-Heu) and melanoma cell lines (NA-8) [124]. Reduced expression of miR-210 in melanoma cells facilitates cell lysis by antigen-specific cytotoxic T lymphocytes (CTLs). Table 1 At a gene regulatory level, PTPN1, HOXA1, and TP53I11 are target genes of miR-210 and are thought to mediate the immunosuppressive response and have been shown to be involved in immune regulation and tumor initiation [125–129]. Another microRNA, miR-34a/c, has been reported to regulate innate immune responses in melanoma cells [109]. miR-34a/c control the expression of ULBP2, which is a ligand for natural killer cell immunoreceptor (NKG2D). NKG2D usually detects early tumors, eliminates

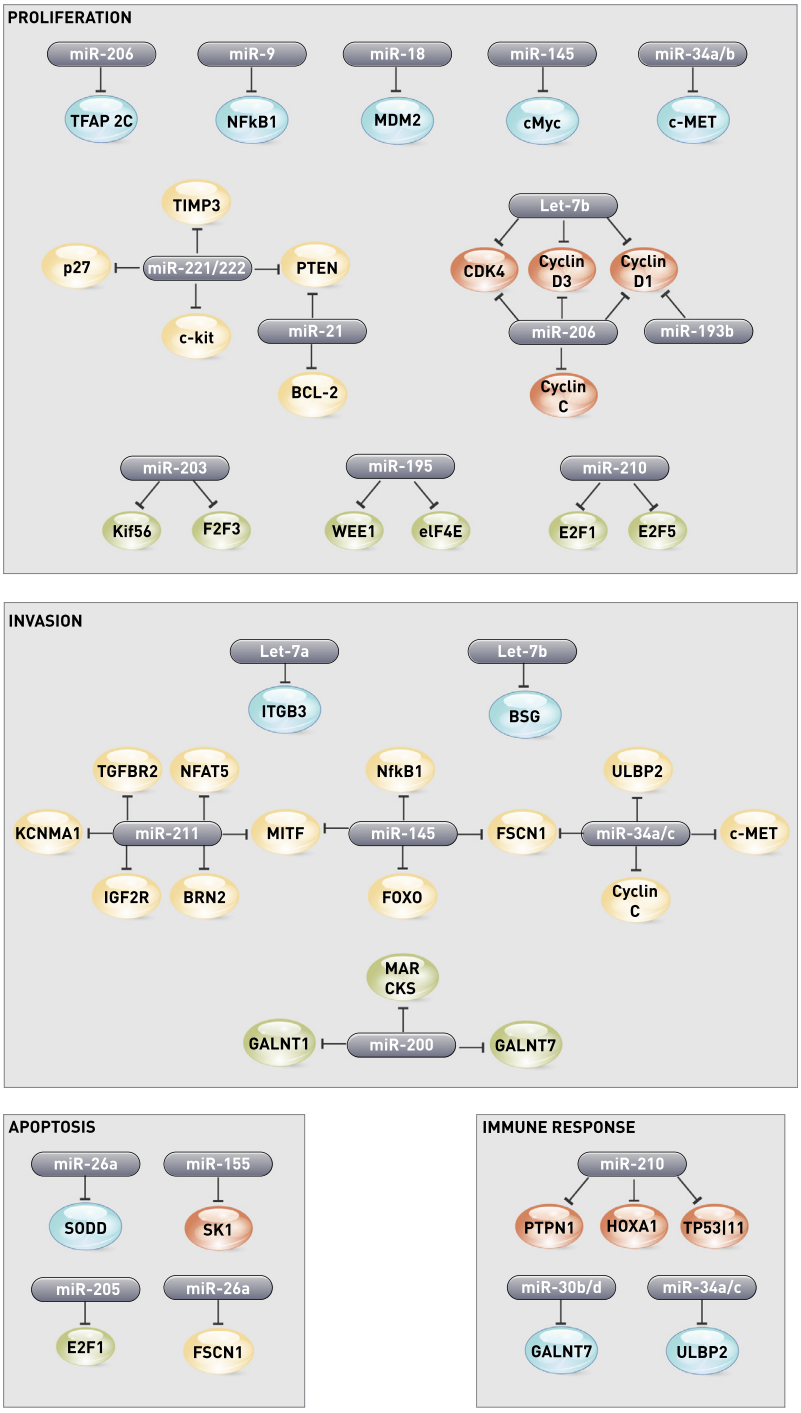

Fig. 1. Schematic representation of the miRNAs involved in proliferation, invasion, apoptosis, and the immune response.

cytotoxic lymphocytes, and provides an innate barrier to tumor development; removal of ligand protects malignant cells from NKG2D-mediated immune surveillance [130,131] and overexpression of miR-34 significantly downregulates ULBP2 expression. In another study, ectopic expression of miR-30b and miR-30 enhanced melanoma metastasis by creating an immunosuppressive environment [113] via GALNT7 and increased synthesis of immunosuppressive molecules such asIL-10, and consequent reduced immune cell activation and recruitment. GALNT7 is a glycosylating protein, and changes in glycosylation patterns are believed to be associated with tumor progression [133]. Similarly, reduced GALANT7 expression levels alter O-glycans which leads to tumor growth and survival and interaction with immune cells [132].

The role of miRNAs in melanoma cell cycle and cell proliferation

Uncontrolled cellular proliferation is a hallmark of cancer. The cell cycle is principally controlled and regulated by cyclin-dependent kinases (CDKs) and the E2F transcription factor [136,137]. Other proteins, such asc-myc, p27, and PTEN, activate CDKs and in turn regulate the cell cycle [138–140]. One can postulate that miRNAs that regulate cell proliferation might directly target these cell cycle regulators. The NF-kB pathway is also known to

Table 1
The miRNAs involved in melanomagenesis.

	Name of miRNA	Expression of miRNAs	Year of reporting	Reference(s) indicating specific role of miRNAs in melanoma	Target	Reference(s) indicating specific role of targeted protein in melanoma
miRNAs involved in proliferation and cell cycle	*let-7b*	Down	2008	[18]	Cyclin D1	[63]
					Cyclin D3	[64]
					CDK4	[65]
	miR-193b	Down	2010	[66]	Cyclin D1	[63]
	miR-145	Down	2014	[67]	c-MYC	
					MITF	[68,69]
	miR-206	Down	2014	[70]	CDK4	
					Cyclin D1	[63]
					Cyclin C	
	miR-221/222	Up	2009	[71]	PTEN TIMP3	[72]
						[73]
			2009	[15]	c-KIT	[74,75]
					p27	[76]
			2008	[17]	c-KIT	[74,75]
					p27	[76]
	miR-205	Down	2011	[77]	E2F1	[78]
					E2F5	[79]
	miR-34a/c	Down	2011	[80]	c-MET	
	miR-9	Down	2012	[81]	NFkB1	[82]
	miR-21	Up	2012	[83]	PTEN	[72]
			2012	[84]	BCL-2	
	miR-203	Down	2012	[85]	F2F3	[86]
					Kif5b	[87]
	miR-195	Down	2013	[88]	WEE1	[89]
	miR-786-3p		2013	[90]	eIF4E	
	miR-214	Up	2011	[91]	TFAP2C	[92]
	miR-15b	Up	2010	[93]		
	miR-126	Down	2013	[94]	ADAM9	[95]
					MMP7	[96]
	miR-18b	Down	2013	[97]	MDM2	[98]
	miR-149	Up	2011	[99]	GSK3α	[100]
	miR-155	Down	2011	[101]	SK1	[102]
miRNAs involved in invasion	*miR-145*	Down	2013	[103]	FSCN1	[104]
	let-7a	Down	2008	[148]	Integrin β3	[105]
	let-7b	Down	2011	[147]	BSG	[106]
	miR-200 family	Down	2010	[107]	MARCKS	[108]
	miR-34a/b/c	Down	2011, 2012	[80,109]	c-MET	[110]
					ULBP2	
	miR-199	Down	2008	[151]	c-MET	[110]
	miR-9	Down	2012	[81]	NfkB1	[111]
	miR-182	Up	2009, 2011	[28,112]	MITF FOXO3	
	miR-30b/d	Up	2011	[113]	GALNT1 GALNT7	[114]
	miR-375	Down	2011	[115]		
	miR-211	Down	2010	[47,52–54]	BRN2, KCNMA1, NFAT5, TGFBR2	
	miR-214	Up	2011	[91]	TFAP2C ITGA3	[92]
	miR-137	Up	2013	[152]	MITF	
	miR-182	Up	2014	[121]	MITF	
miRNAs involved in apoptosis	*miR-15b*	Up	2010	[93]		
	miR-155	Down	2009, 2009	[101,116]	SK1	[102]
	miR-211	Down	2010	[47]		
	miR-26a	Down	2013	[117]	SODD	[118]
	miR-768-3p	Down	2014	[90]		
	miR-21	Up	2012	[83]		
miRNAs involved in epigenetics	*Global effect*		2013	[119]		
	miR-375		2011	[115]		
	miR-34b	Down	2011	[120]		
	miR-182	Up	2014	[121]		
	miR-34a	Up	2008	[154]		
	miR-137	Down	2011	[122]		
	miR-29c	Down	2011	[123]	DNMT3A DNMT3B	
	miR-31	Down	2012	[151]		
	miR-18b	Down	2013	[97]		
miRNAs involved in the immune response	*miR-210*	Up	2012	[124]	PTPN1 TP53I11	[125,126]
			2012	[124]	HOXA1	[127,128]
						[129]
	miR-34a/c	Down	2012	[109]	ULBP2	[130,131]
	miR-30b/d	Up	2011	[113]	GALNT7	[132,133]

be associated with proliferation in melanoma [141], and it is also well-documented that cyclin D1, cyclinD3, and CDK4 play an important role in tumor progression [63–65,142].

let-7b is an miRNA known to target cell cycle regulators. Acting as a tumor suppressor, increased let-7b expression results in significantly decreased proliferation [18] via reduced gene and protein expression of CDK4, cyclin D1, and cyclin D3 [49]. miR-193b targets cyclin D1 (CCND1) and is significantly downregulated in melanocytic nevi [66]. Increased expression of miR-193b in melanoma cell lines (Malme-3M cells) significantly reduces CCND1 gene and protein expression and inhibits proliferation of melanoma cells.

Elevated expression of miR-145 in canine and human melanoma cell lines significantly reduces proliferation [143] via targeting of c-MYC [143] or Erbb3 [144]. It has been also recently been shown that miR-206 is significantly downregulated in melanoma cells and reduces cell growth and migration in many melanoma cell lines by targeting cell cycle proteins including CDK4, cyclin D1, and cyclin C [70].

Some microRNAs indirectly control the cell cycle via p27 [76], a tumor suppressor protein that binds to, and inhibits the function of, the cyclin D1-CDK4 complex and in doing so acts as a key regulator of the G1-S cell cycle transition; indeed, reduced expression of p27 is one of the main causes of uncontrolled cell-cycle progression into S phase [145]. Two studies have shown that miR-221/222 directly target p27 and is involved in cell cycle regulation [15,17]; increased proliferation was observed in melanoma cells overexpressing miR-221/222, with the opposite true both *in vitro* and *in vivo* [15,17]. Furthermore, the same studies show that miR-221/222 target the oncogenic tyrosine kinase receptor c-kit [74,75]. Garofalo et al. [71] showed that miR-221/222 targets the PTEN and TIMP3 tumor suppressors [72,73], induces TRAIL-mediated resistance, and enhances migration via activation of the AKT/PI3K signaling pathway and metallopeptidases.

Other miRNAs, including miR-205, miR-149, miR-18b, miR-21, miR-203, and miR-26a, also regulate cell cycle proteins but in a cyclin-independent manner. Dar et al. [77] showed that in primary melanomas, the expression of miR-205 was significantly reduced and inversely correlated with melanoma progression. Overexpression of miR-205 significantly reduced melanoma cell proliferation and colony formation *in vitro* and tumor growth *in vivo,* and induced a senescent phenotype [77] and apoptosis via the E2F1 transcription factor [146]. miR-205 targets the E2F1 and E2F5 transcription factors known to play a critical role in malignant melanoma [78,79]. Jiang et al. [83] studied 106 primary melanomas and metastases and showed that inhibition of miR-21 was significantly associated with increased apoptosis and growth of human cutaneous melanoma, via inhibition of PTEN, Akt phosphorylation, Bax upregulation, and Bcl-2 inhibition. Satzger et al. [84] similarly determined that miR-21 is upregulated in primary melanomas and melanoma cell lines, and miR-21 knockdown in melanoma cell lines induced apoptosis, but not proliferation. miRNA-203 plays a crucial role in cell cycle arrest, and has been shown to be expressed at reduced levels inhuman and canine malignant melanoma cells and inhibits cell cycle arrest and the senescence phenotype. miR-203 might induced cell cycle arrest and senescence via an E2F3-dependent mechanism [85], kinesin superfamily protein 5b (kif5b), or the MITF/Rab27a pathway, which is one of the main pathways active in melanoma cells [67]. miR-195 was shown to be downregulated in primary melanomas and to target WEE1 [89]. Ectopic expression of miR-195 in melanoma cell lines reduced WEE1 expression and stress-induced G2-M cell cycle arrest and increased proliferation. A few other studies have demonstrated a role for miR-786-3p, miR-214, miR-15b, miR-155, and miR-126 in cellular proliferation; miR-786-3p has been shown to regulate proliferation and apoptosis by targeting the eukaryotic translation initiation factor 4 (eIF4E) in melanoma cells [90], overexpression ofmiR-214 targets the adhesion receptor ITGA3 and reduces cell death [91], and downregulation of miR-15b reduced proliferation and increased apoptosis [93].

Two miRNAs have been shown to regulate the cell cycle by targeting p53. miR-18b suppresses proliferation and overexpression leads to suppression of the proto-oncogene MDM2 [98], activation of the p53 pathway, and reduced survival of melanoma cells [97]. miR-149 has been shown to effect cell cycle via a p53-mediated mechanism; p53 regulates miR-149, which in turn targets glycogen synthase kinase-3α (GSK3α) [100], increased expression ofMcl-1, and ultimately resistance to apoptosis [99]. Greenberg et al. [80] sought to identify those miRNAs that regulate the aggressive phenotype of melanoma using a comparative high-throughput miRNA profiling approach; two isogenic human melanoma cell lines were molecularly and phenotypically profiled and shown to display major differences in their capacity for proliferation, invasion, and tube formation.

miR-9 has been shown to be downregulated in metastatic melanomas compared to primary melanomas [81], and overexpression of miR-9 in melanoma cells resulted in significantly decreased proliferation and migration via an NF-kappaB1-dependent mechanism. Levati et al. demonstrated that ectopic expression of miR-155 significantly inhibits proliferation and induces apoptosis in four melanoma cell lines [101]. miR-126 is also thought to play a vital tumor suppressor role in human melanoma; Felli et al. [94] showed that miR-126 & 126* expression were downregulated during melanoma progression, and two metalloproteases, metalloprotease domain 9 (ADAM9) and metalloprotease 7 (MMP7), were identified as direct targets of miR-126 & 126*, both of which are thought to be involved in melanoma progression [95,96].

The role of miRNAs in melanoma cell invasion

Many factors are known to drive melanoma cell migration and invasion, including FSCN1, BSG, β3-integrin, MARKS, GALANT7, c-MET, and NFkB [104–106,108,110,111]; a number of miRNAs are thought to target these proteins and pathways. *miR-145*is thought to downregulate fascin actin-bundling protein 1 (FSCN1), a known regulator of cell migration [103,104]. Segura et al. [28] investigated the role of *miR-182* in melanoma cell invasion and showed that miRNA genes are located in genomic regions that harbor frequent gains and losses in primary melanomas [3,28]. *miR-182* was differentially expressed in melanoma cell lines compared to benign melanocytes, and *FOXO3* and *MITF* were shown to be direct targets of miR-182 [28] and contribute in the migratory and invasive potential of the SK-MEL melanoma cell line.

In a mouse model of liver metastasis, immunocompromised mice received intra-splenic injections of A375 melanoma cells and subsequently intra peritoneal injections of chemically modified anti-*miR-182* or negative control anti-miRNA [112]. Treatment of mice with anti-*miR-182* resulted in significantly fewer liver metastases compared to controls. Similar findings were observed when mice were pre-treated with three doses of anti-*miR-182* oligonucleotides followed by three weeks of *miRNA-182*. Suppression of *miR-182* gene expression in liver tissues was verified by real-time PCR and was accompanied by upregulation of the *miR-182* targets *ADCY6* and *FOXO3*. Moreover, mRNA expression profiles of anti-*miR-182*-treated tumors differed from those of controls, supporting the notion that anti-*miR-182* has a transcriptional impact on gene expression. Differentially expressed genes included genes involved in cell adhesion, migration, and apoptosis; upregulated genes after anti-*miR-182* treatment included *NFASC, CASP2, NCAM1,* and *CLDN17*. CASP2, already identified as a *miR-182* target [28], is a member of the caspase family of pro-apoptotic genes. Overall, the treatment of mice was well tolerated with no gross abnormalities

and only slight derangement of liver function. The authors concluded that *miR-182* targeting might be a promising therapeutic strategy for metastatic melanoma.

Gaziel-Sovran et al. [113] demonstrated that the invasive capability of two melanoma cell lines (113/6-4L and 131/4-5B1) was mediated by expression of *miR-30b* and *miR-30d*, which regulated invasion but not proliferation. The *miR-30b/30d* cluster is located near to *c-MYC* (8q24.21), an archetypal oncogene. Global transcriptomic analysis showed differential expression of 784 genes, with 58 genes downregulated in both cell lines. The most highly downregulated targets were *GALNT1*, GALNT7, and SEMA3A. Microarray analysis further revealed that ectopic expression of miR-30d upregulated the expression of immune modulators, such as IL-10, via repression of GALNT7 by miR-30d.

It has been shown that *let-7b* targets basigin (BSG), an invasion-associated protein [106]. Reduced *let-7b* expression in melanoma cells leads to increased metastases due to enhanced expression of BSG and consequently enhanced expression of extracellular matrix metalloproteinases (MMPs). Overexpression of *let-7b* resulted in reduced BSG and MMP-9 protein expression and reduced distant metastases [147]. *let-7a* targets *ITGB3*, which is known to increase the invasiveness of melanoma cells [105], and increased *ITGB3* expression due to depletion of *let-7a*has been shown to increase the invasive potential of melanoma cells [148]. Schwab et al. [107] showed that reduced expression of *miR-200* family members promotes invasion and metastasis by adapting the cell to different local microenvironments via two inter-convertible modes of invasion: elongated mesenchymal-type and rounded amoeboid-like. These morphological changes were phenocopied by reducing expression of the *miR-200c* target, *MARCKS*, which is involved in the formation of cell protrusions [108].

The expression of c-MET is associated with cell invasion and inhibition of apoptosis; it is also a prognostic factor in clinical studies [149,150]. *miR-199* and *miR-34b/c* have been shown to target MET and decrease its mRNA and protein expression, and inhibition of *miR-199* and *miR-34b/c* increase expression of MET and increased cell adhesion and migration [151]. *miR-137* has also been shown to target c-Metand YB1, with functional studies indicating that *miR-137* suppresses melanoma cell invasion and vice versa [152].

Role of miRNAs in apoptosis

Many studies have highlighted the role of microRNAs in apoptosis, including *miR-26a*, *miR-155*, *miR-205*, *miR-768-3p*, *miR-21*, *miR-15b*, *miR-126*, the *miR-506-514* cluster and *miR-149*. Reuland et al. [117] showed that *miR-26a* was downregulated in melanoma cell lines compared to primary melanocytes, and overexpression of *miR-26a* caused significant and rapid cell death and repressed expression of *SODD* [118], which protects melanoma cells from apoptosis. *miR-155* was also shown to be down regulated in melanoma cells compared to normal melanocytes [101,116], and ectopic expression of *miR-155* significantly inhibited proliferation and induced apoptosis by targeting SKI, a transcriptional coregulator; downregulation of SKI *in vitro* inhibited melanoma cell growth [102]. *miR-205* expression was reduced in melanoma cells compared to nevi [77], with further analysis showing that *miR-205* targets and reduces expression of E2F1, thereby decreasing proliferation and inducing apoptosis or, as shown in [78], via its capacity to activate p73 family members in advanced malignant melanomas.

Role of miRNAs in melanoma epigenetics

Epigenetics refers to the biological process by which changes in phenotype or gene expression occur without changes to the DNA sequence. Cellular epigenetic events occur at greater frequency than mutations, may be sustained during the life of the cell, and can be transmitted to progeny [153].

Our group has conducted the most comprehensive characterization of the role of epigenetics in melanoma development. Using next generation sequencing (NGS), were ported on a global analysis of methylation events occurring in melanoma cell lines and melanocytes [119]. The CpG islands in the upstream regulatory regions of many coding and non-coding RNA genes, such as *TERC*, were hypermethylated, while repeated elements, such as LINE-2 and LTR, showed widespread hypomethylation in advanced stage melanoma cell lines; these results are currently being validated in human patient samples. We demonstrated that *miR-375* is epigenetically regulated in melanoma cells and patient samples [115]; CpG island methylation regulated expression of *miR-375* in WM1552C melanoma cells after treatment with the demethylating agents, 5-aza-2-deoxycytidine and 4-phenyl-butyrate (4-PBA). Methylation of *miR-375* CpG islands was stage dependent and was significantly greater in stage II and III melanoma cell lines compared to stage I melanoma lines or benign melanocytes. In a third study, regulation of *miR-34b* by CpG island methylation was investigated, and increased methylation was apparent in stage III and IV melanoma cells compared to stage I and II melanoma cells, melanocytes, and keratinocytes [120].

miR-182 has been shown to be overexpressed in human melanoma cells after epigenetic modulation, and CpG islands upstream of mature *miR-182* were hypermethylated in melanoma cells [121]. Similar work was carried out by Lodygin et al., [154] which demonstrated that expression of *miR-34a*, target of the tumor suppressor gene p53, was highly reduced in various cancers due to aberrant CpG methylation of miR-34a promoter. Apart of other cancers, CpG methylation of *miR-34a* promoter was detected in melanoma cell lines (19/44; 43.2%) and primary melanoma (20/32 samples; 62.5%). Expression of *miR-137* was much lower in uveal melanoma than in uveal melanocytes [122], with ectopic expression of *miR-137* reducing cell growth and significantly reducing expression of MITF, c-Met, and CDK6. From an epigenetic perspective, *miR-137* expression was significantly increased with treatment with 5-aza-2-deoxycytidine and trichostatin A, indicating a potential role in epigenetic regulation. It has also been shown that *miR-29* downregulates the DNA methyltransferases, DNMT3A and DNMT3B, which have been reported to be essential for methylation of the promoter region of tumor-related genes [123]. High expression of *miR-29c* was inversely correlated to both DNMT3A and DNMT3B protein expression in melanomas, and the authors concluded that both *miR-29c* and DNMT3B play an important role in melanoma progression and may be useful as epigenetic biomarkers. Another microRNA *miR-31* was observed to be down regulated in melanoma tumor and cell lines. The authors of the study put forward three possible reasons for the reduced expression of *miR-31*. One reason was the genomic loss in a subset of samples, second reason was the epigenetic silencing by DNA methylation and third reason was EZH2-mediated histone methylation [155]. Dar et al., [97] targeted the MDM2-p53 pathway to investigate the biological role of *miR-18b* in melanoma. They demonstrated that expression of *miR-18b* was substantially reduced in melanoma specimens and cell lines due to hypermethylation and was reinduced in melanoma cell lines after 5-AZA-deoxycytidine treatment by 1.5 to 5.3-fold.

miRNAs as biomarkers for the diagnosis and prognosis of patients with melanoma

There is promise that measuring the expression of circulating miRNAs could be used to diagnose and determine the prognosis of a number of cancers [156–159]. Similarly, in melanoma patients, circulating miRNAs in the serum have been proposed as potential

biomarkers. Recently, Shiiyama et al. [160] examined the expression profiles of 2000 miRNAs in the serum of melanoma patients and identified six microRNAs (*miR-9*, *miR-145*, *miR-150*, *miR-155*, *miR-203*, and *miR-205*) that were differentially expressed in metastatic melanoma patients compared to normal individuals. Similarly, in another study, five miRNAs, *miR-150*, *miR-15b*, *miR-339*, *miR-199a-5p*, and *miR-424* were highly and differentially expressed in the serum of melanoma patients with a high risk of recurrence. The diagnostic accuracy of identification of primary melanomas using serum miRNA measurements has also been tested by screening 900 human miRNAs in 24 blood samples from melanoma patients and 20 samples from normal individuals [161]; 51 miRNAs showed dysregulated expression in the serum of melanoma patients [162]. One study focused on *miR-221*, and found significantly upregulated expression of *miR-221* in malignant melanoma patients compared to healthy individuals [163]. miRNA transcriptomic analysis of tissue biopsies of nevi, thick primary melanomas, and metastatic melanomas were analyzed using the Illumina NGS platform, and again *miR-211*was identified as having reduced expression in melanomas vs. nevi [164].

miRNA biomarker profiling has also been attempted in tissue samples of melanomas resected from patients for diagnosis purposes, including from formalin-fixed paraffin-embedded (FFPE) samples commonly used in diagnostic pathology laboratories. These studies identified a number of miRNAs that may be suitable diagnostic biomarkers for melanoma [165–167].

The utility of miRNAs as prognostic biomarkers in melanoma has also been investigated in a number of studies. In a pioneering study, the metastases in patients with uveal melanoma were investigated through microarray analysis and classified into low and high metastatic risk groups. The most significant expression was observed for *let-7b* and *miR-199a* and may be utilized as biomarker for metastatic risk in uveal melanoma [168]. Satzger et al. [93] studied 128 primary melanomas and identified differential expression of three miRNAs, *miR-15b*, *miR-210*, and *miR-34a*, the first two being upregulated and the latter downregulated in melanomas compared with melanocytic nevi; only miR-15b expression was associated with the poor recurrence-free survival. Xu et al. [49] revealed that out of 20 miRNAs that exhibited differential expression in primary or metastatic melanomas in comparison to benign nevi, only two miRNAs, *miR-203* and *miR-205*, were significantly upregulated in malignant lesions and could be used as a biomarker for prognostic or diagnostic purposes.

Two recently published reports have focused on NGS for the identification of miRNAs with potential use as diagnostic biomarkers in patients with melanoma. In the first study of 698 known miRNAs, seven miRNAs (*miR-203*, *miR-204-5p*, *miR-205-5p*, *miR-211-5p*, *miR-23b-3p*, *miR-26a-5p*, and *miR-26b-5p*) showed decreased expression in melanomas vs. nevi [164]. In the second study [169], four differentially expressed miRNAs (*hsa-miR-146*, *hsa-miR-27*, *hsa-miR-877*, and *hsa-miR-186*) were detected in metastatic melanomas and primary cutaneous melanoma samples [169]. The miRNAs that have been investigated as biomarkers are shown in Table 2.

miRNAs as therapeutic agents

Recently, the focus of miRNAs in melanoma in translational research has shifted towards their use as therapeutic agents. Reuland et al. [117] identified *miR-26a* as significantly downregulated in human melanoma cells and established that the silence of death domain (SODD) may act as a novel target site for *miR26a* that mediates melanoma cell death. *miR-26a* may therefore serve as potential therapeutic molecule in the treatment of melanoma.

Wagenseller et al. [170] studied global miRNA expression profiles in melanoma tissues using microarrays in patients treated with anticancer drug and angiogenesis inhibitors, temsirolimus and bevacizumab [171,172]; there was significant upregulation of 15 miRNAs in treated vs. non-treated tissues, 12 of which having tumor suppressor function via the targeting of 15 oncogenes. These miRNAs are therefore attractive candidates for further investigation as therapeutic agents.

The role of lncRNAs in melanoma

lncRNAs are very similar to mRNAs and are mainly regulated by RNA polymerase II. Like mRNAs, they are spliced, capped, and polyadenylated, but they do not have protein-coding capacity. The first functional lncRNA, *XIST*, was discovered in the early 1990s [173–175]; until then, lncRNAs were generally regarded as transcriptional noise or junk sequences. Recent studies have illustrated several important functions of lncRNAs in many biological processes, including regulation of gene expression, dosage compensation, genomic imprinting, nuclear organization and compartmentalization, and nuclear to cytoplasmic trafficking [176,177], and more functions are likely to be discovered in the future.

Table 2
The miRNAs involved in prognosis, diagnosis, and therapeutics.

	Type of biomarker	Name	Expression	Year	References
Prognostic and diagnostic miRNAs	Circulating miRNAs	*miR-9, miR-145, miR-150, miR-155, miR-203, miR-205*	Upregulation	2013	[160]
		miR-150, miR-15b, miR-339, miR-199a-5p and miR-424	Upregulation	2012	[161]
		Identification of 51 miRNAs	Dysregulation	2010	[162]
		miR-221	Upregulation	2011	[163]
	miRNAs in solid tumors	Identification of 84 miRNAs		2009	[165]
		Identification of 70 miRNAs	Dysregulation	2009	[167]
		let-7b	Downregulation	2008	[168]
		miR-199	Upregulation	2008	[168]
		miR-203, miR-204-5p, miR-205-5p, miR-211-5p, miR-23b-3p, miR-26a-5p and miR-26b-5p	Downregulation	2013	[164]
		miR-146, miR-27 miR-877, miR-186		2014	[169]
		miR-203	Upregulation	2012	[49]
		miR-205	Upregulation	2012	[49]
		miR-15b	Upregulation	2010	[93]
		miR-210	Upregulation	2010	[93]
		miR-34a	Downregulation	2010	[93]
Therapeutic miRNAs		Identification of 15 miRNAs	Upregulation	2013	[170]
		miR-26a	Downregulation	2013	[117]

Table 3
List of lncRNAs currently implicated in melanoma.

Name	Cell utilized	Expression	Type of lncRNA	Role of lncRNA	Year of reporting	References
SPRY4-IT1	WM1552C	Upregulated	Antisense long non-coding RNA	Regulation of cells viability apoptosis and melanoma cell motility	2011, 2014	[178] [182]
BANCR		Upregulated	lincRNA	Migratory capacity of melanoma cells by regulating CXC11	2012	[179]
HOTAIR			lincRNA	Motility, invasion, and metastasic potential of metastatic melanoma	2013	[180]
LIME23	YUSAC melanoma cell line	Upregulated	lincRNA	Regulate process of melanoma through binding of PSF	2013	[184]
TUG1			lincRNA	–	2013	[188] (Article withdrawn)
ANRIL	Human blood cells	Upregulated	Antisense long non-coding RNA	Risk of melanoma due to SNPs in 9P21 region	2011	[186]
GAS5		–	–	Malignant melanomas due to special break points at 1p36 and at several sites throughout 1p22-q21	2000	[187]

In contrast to miRNAs, there is a paucity of literature discussing the role of specific lncRNAs in melanomas. In the seminal lncRNA melanoma study by Khaitan et al. [178], 77 lncRNAs were identified as significantly dysregulated in the melanoma cell line WM1552C and in primary melanomas from patients. A more detailed study was carried out on *SPRY4-IT1*, an intronic lncRNA of the SPRY4 gene, and knockdown of *SPRY4-IT1* in the melanoma cell lines A375 and WM1552C resulted in significant cell death, invasion, and induction of apoptosis. Dysregulation of *SPRY4-IT1* may therefore have an important role in melanomagenesis, be used as an early biomarker, and be a key regulator for melanoma pathogenesis in humans. This study formed the basis for investigation of various other lncRNAs in melanoma [179,180] and stimulated interest in the role of *SPRY4-IT1* in other cancers [181]. Follow-up studies have detailed the mechanistic role of *SPRY4-IT1* in melanoma cells and shown that ectopic expression of *SPRY4-IT1* in normal human melanocytes forms multinuclear, multidendrite structures [182] .

In another study, the lncRNA *HOTAIR* was shown to be overexpressed in metastatic tumor in lymph nodes compared to matched primary melanomas [180]. Knockdown of *HOTAIR* suppressed metastases and resulted in a three-fold reduction in the invasiveness of the melanoma cell line A375. A wound healing assay indicated better healing in cells transfected with control constructs than those transfected with *HOTAIR* in A375 cells [180]. Suppression of matrix degradation using *HOTAIR* knockdown upregulated the MMPs required for metastasis [183], which was confirmed by elevated gelatinase activity.

Wu et al. [184] showed that aberrant expression and increased binding of the lncRNA *Llme23* to polypyrimidine tract-binding protein-associated splicing factor (PSF) was associated with mouse and human tumors through repression of proto-oncogene Rab23. *Llme23* knockdown suppressed the malignant properties of the human melanoma cell line YUSAC and repressed expression of the proto-oncogene *Rab23* [185].

In one study, 39 differentially regulated lncRNAs were identified by Flockhart et al. [179] in *BRAF* V600E melanomas cells, and the *BANCR* lncRNA was found to be overexpressed and associated with malignant melanoma. *BANCR* knockdown reduced melanoma cell migration by upregulating the chemokine CXCL11, a mediator of cell migration. This elegant study was an important discovery of an oncogene-regulated lncRNA transcript of potential clinical relevance in cancer.

Pasmant et al. identified single nucleotide polymorphisms (SNPs) on chromosome 9p21 that were associated with melanoma and other diseases through the allelic expression of the lncRNA *ANRIL* [186]. Expression studies have confirmed the coregulation of p15/CDKN2B, p16/CDKN2A, p14/ARF, and ANRIL. ANRIL in involved in regulation of CDKN2A/B expression through a cis-acting mechanism and its implication in proliferation and senescence. Modulation in ANRIL expression mediated susceptibility to several important human diseases, including melanoma. Similarly, genetic aberrations of the *GAS5* locus have been found in several tumors, including melanoma, breast, and prostate cancers [187]. A list of all the lncRNAs currently implicated in melanoma is shown in Table 3.

Conclusions

Although many drugs have been introduced for the treatment of melanoma, clinical outcomes for metastatic disease remain poor and resistance to therapy is common. An increased understanding of the molecular and cellular biology of non-coding RNAs shows promise for the diagnosis, prognosis, and treatment of patients with melanoma. Although there is a lot of data relating to miRNAs in melanoma, more work is required to develop sensitive and specific molecular tests. To achieve this goal, there needs to be focused attention on the early diagnosis of melanoma recurrence, which is devastating for the patient. While established imaging techniques, such as MRI, PET, and CT are being used to detect early stage cancer, they lack the sensitivity required for very early tumor detection [189], in contrast to molecular-based techniques.

lncRNAs might also be used as biomarkers for the early diagnosis of melanomas. An optimal approach might be by using a combination of miRNAs and lncRNAs for the diagnosis and treatment of melanoma. The combinatorial approach will focus on protein genes that are generally oncogenes and are involved in melanoma progression and are generally targeted by miRNAs as well as role on lncRNAs which are beginning to become major molecules in cancer detection and treatment especially melanoma. Our group has performed extensive research on the early detection of melanoma using both miRNAs and lncRNAs, and the combination of these approaches might offer a solution for achieving this goal in the near future.

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