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Predictive Capacity and Functional Significance of MicroRNA in Human Melanoma

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1. Introduction

Melanoma is one of the most serious forms of cutaneous malignancies with an incidence of over two million people worldwide[1]. During 2010, an estimated 68,130 new patients were diagnosed with melanoma, and 8,700 deaths were attributed to the development of metastatic disease in the United States[2]. Compared to earlier stages of melanoma, the prognosis for patients with metastatic (stage IV) melanoma is very poor with six out of every seven skin cancer-related deaths being attributed to melanoma. However, our diagnostic and prognostic methods for melanoma are primarily histologic, such as Breslow's depth of invasion, falling far short of being able to accurately predict the overall survival, recurrence risk, or clinical outcomes for patients[3]. There are several methods of treatment for metastatic melanoma, including radiation therapy, immunotherapy, chemotherapy, and palliative surgery[2, 4, 5]. However, there exists a clear and unfortunate understanding that these therapies are only minimally effective in treating patients with advanced disease[6].

MicroRNAs(miRNAs) are a set of small, average 22 nt in length, single-stranded, non-protein-coding RNA molecules that can recognize and bind 3'-untranslated regions (UTR) of mRNA, blocking translation of the gene or inducing cleavage of the mRNA[7, 8]. To date, a total of 15,172 miRNAs (Version 16.0), including 1,049 human miRNAs, have been registered in the miRbase database. The biogenesis of miRNA is similar to the other RNA starting from DNA transcription. A primary miRNA (pri-miRNA) is an independent transcript processed by RNA polymerase II (Pol II), which are bound in the nucleus by the microprocessor complex consisting of the RNase III-type endonuclease, Drosha, and its co-factor, Pasha (DGCR8). These enzymes can crop the pri-miRNA into a hairpin loop, cleaving off 3' and 5' regions of excess mRNA to give precursor miRNA (pre-miRNA) ~70 nt in length. Pre-miRNA is then actively transported to the cytoplasm by exportin-5 where it is bound by the RNAse III-type endonuclease, Dicer, which removes the loop, resulting in a duplex of complementary, mature miRNA sequences. One strand is bound by the RNA-induced silencing (RISC) complex, which guides mature miRNA to target mRNA for subsequent silencing. The remaining strand is usually degraded, but it may be bound by RISC and target its own mRNAs, which are denoted with an asterisk (i.e., miR-10b and miR-10b*)[9, 10].

In both plants and animals, miRNAs are capable of mediating gene expression by influencing the RNA's stability and/or translational resspression[11, 12]. Impressively, a single

miRNA can potentially bind hundreds to thousands of its cognate mRNA 3'UTR sequences. It is predicted that miRNAs may regulate upwards of 30% of all mammalian genes' expression, due to their critical function in gene regulation and expression[8]. Thus, it is meaningful to understand their roles and significance in the essential cellular events, such as development, differentiation, proliferation, and apoptosis, which account for carcinogenesis, tumor progression, and metastasis[13-16]. MiRNA synthesis and function is summarized in Figure 1.

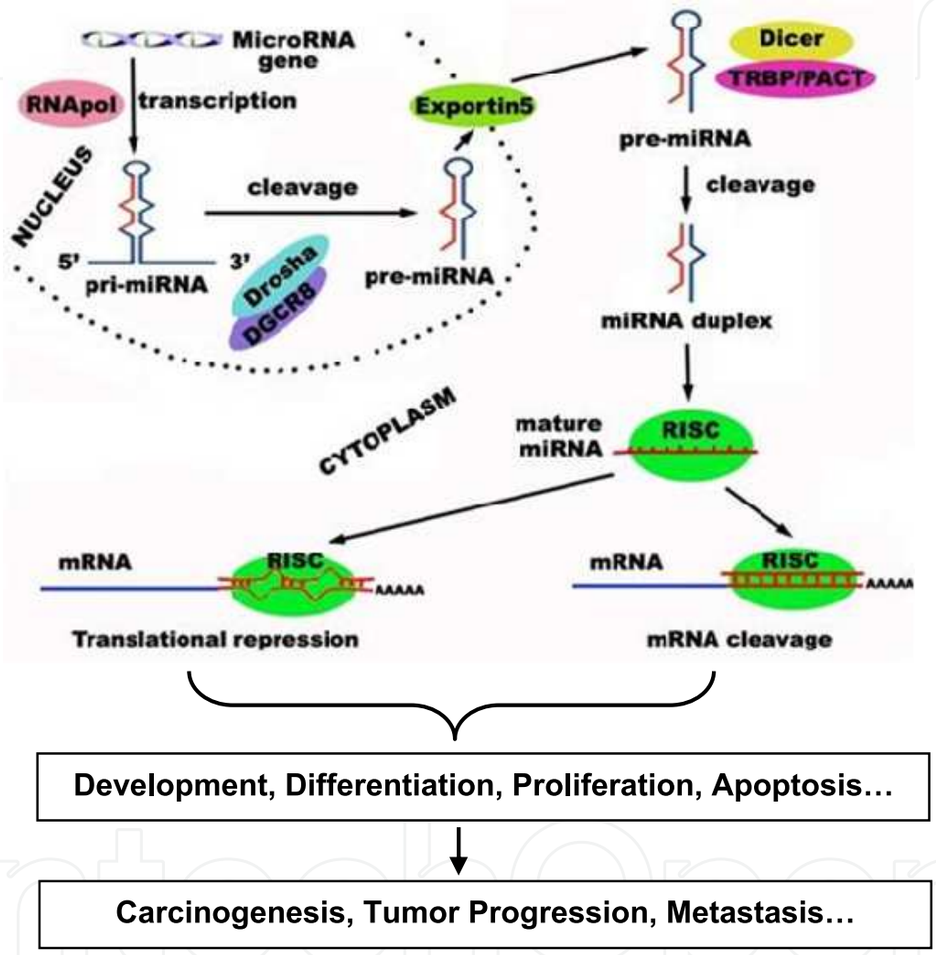

Fig. 1. MicroRNA biogenesis and biological functions

Following a pilot study connecting B-cell chronic lymphocytic leukemia (CLL) and deregulated expression of miR-15a and miR-16-1[17], it has been demonstrated that more than 50% of miRNA genes are located in cancer-associated genomic regions or within fragile sites[18], and more and more miRNAs have been identified to play a central role in the pathogenesis of human cancers. Although it was in 2006 that the first study on miRNA in melanoma has reported that 86% of primary melanoma cell lines had DNA copy number alterations in genomic loci containing miRNA genes[19], studies focusing on the roles of miRNA in the pathogenesis and development of melanoma have bloomed since 2008. Figure 2 illustrates the miRNAs reported by more than two studies or confirmed by

functional studies in the progression of melanoma[20-26], suggesting that miRNAs play an important role in melanocyte and melanoma biology. To date, there are 77 publications that can be retrieved in PUBMED when using keywords "melanoma and miRNA"; more than 99% of them were published in the latest three years, and half of them were published from 2010 to 2011, which is evidence that this research field is rapidly expanding. However, a few knowledge and understanding gaps need to be filled before taking full advantage of miRNA signatures in melanoma research. In 2010, we were invited to author a review summarizing the accomplishments on the research of miRNA and melanoma[27]. Here, based on the previous review, we will highlight the latest progress in this field.

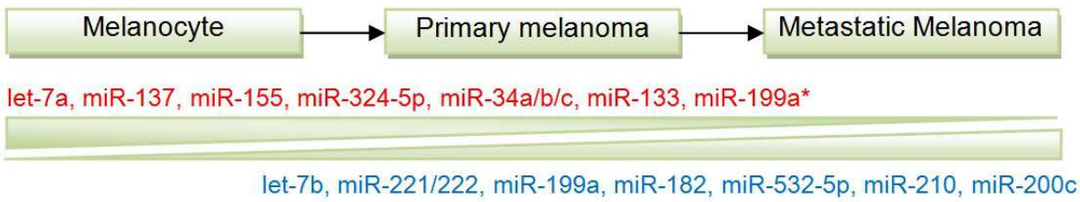

Fig. 2. Representative miRNAs involved in the progression of melanoma

2. Oncogenic miRNAs in melanoma

The role of miRNAs in tumorigenesis depends on their target genes' classification and abundance. When targeting tumor suppressor genes, these over-expressed miRNAs will play the promoting tumor roles as oncogenes; likewise, when targeting oncogenes, these miRNAs will have the characteristics of tumor suppressors. Kitago et al. reported that miR-532-5p directly targeted the runt-related transcription factor 3 (RUNX3) tumor suppressor during the progression from melanocyte to metastatic melanoma[28]. MiR-532-5p was shown to be significantly up-regulated in melanoma cells compared to normal melanocytes and in metastatic melanoma tissue compared to primary melanoma tissue. The transfection of anti-miR-532-5p molecules to the melanoma cells rescued the expression of RUNX3. Methylation analysis of the RUNX3 promoter region showed that transcriptional regulation was not a major regulatory mechanism for the down-regulation of RUNX3 expression in melanoma, suggesting miR-532-5p induced post-transcriptional regulation played an important role in melanoma progression.

Zhang et al. demonstrated that the expression of miR-210, the most prominent miRNA up-regulated by hypoxia and a direct transcriptional target of hypoxia inducible factors (HIFs), was elevated in multiple cancer types and correlated with breast cancer and melanoma metastases, respectively. MiR-210 over-expression in cancer cells bypassed hypoxia-induced cell-cycle arrest by directly targeting the expression of MNT, which is a gene known as one of the Myc antagonists. The miR-210-mediated abolishment of hypoxia-induced cell-cycle arrest was restored by the loss of Myc[5]. This finding indicated that miR-210 influenced the hypoxia response in tumor cells by triggering a Myc-like response by targeting MNT expression.

The miR-200 family has received much attention for suppressing epithelial-mesenchymal transition (EMT) as well as their down-regulation in some tumors promotes invasion and metastasis. Interestingly, Elson et al. showed that levels of miR-200 are increased in melanoma cell lines compared to normal melanocytes. In melanoma cell lines, the expression of miR-200 members has no significant effect on suppressing invasion but

instead leads to a switch between modes of invasion. For example, miR-200c results in a higher proportion of cells thus adopting the rounded, amoeboid-like mode of invasion by reduced expression of myristoylated alanine-rich protein kinase C substrate (MARCKS); meanwhile, miR-200a results in a protrusion-associated elongated mode of invasion by reduced actomyosin contractility. This study improved our understanding of the impacts of the miR-200 family on suppressing invasion and metastasis, and implied a novel insight of these miRNAs in melanoma[29].

3. Tumor suppressor miRNAs in melanoma

Recently, miR-34 was identified as a target and a potential key responder of the tumor suppressor gene product, p53. Ectopic expression of miR-34a induced a G1 cell-cycle arrest, senescence, and apoptosis, which suggested that miR-34 was a potential tumor suppressor[12]. The altered expression of miR-34 was also found in melanoma progression[22, 24, 30]. Lodygin et al. reported that miR-34a expression is silenced in several types of cancer due to the aberrant CpG methylation of its promoter. Reportedly, 43.2% of melanoma cell lines and 62.5% of primary melanoma samples displayed CpG methylation of the miR-34a promoter and loss of miR-34a expression, whereas the two samples of normal melanocytes included in the study did not show promoter methylation[30]. Migliore et al. identified three miRNAs, miR-34b, miR-34c, and miR-199a*, in melanoma cells that negatively regulate the expression of MET, which is an oncogene that encodes the tyrosine kinase receptor for hepatocyte growth factor[24]. MET is frequently over-expressed in many human tumors and promotes the 'invasive growth' that results from the stimulation of cell motility and protection from apoptosis. Exogenous expression of these miRNAs in primary melanoma cells led to a decreased MET protein expression and resulted in the impairment of MET-mediated motility in these cells[24]. Recently, Yan et al. detected the expression level of miR-34a in uveal melanoma cells and melanocytes and found that miR-34a had been actively expressed in melanocytes but not in uveal melanoma cells. Additionally, the transfection of miR-34a into melanoma cells led to a significant repression of their growth and migration by down-regulating the expression of c-Met directly and the expression of phosphorylated Akt (p-Akt) and other cell-cycle-related proteins indirectly [22].

Mazar et al. found the levels of miR-211 were reduced in melanoma cell lines compared with expression levels in melanocytes. Ectopically expressing miR-211 in different melanoma cell lines caused significant growth inhibition and reduced invasiveness by cleaving the mRNA and inhibiting the translation of KCNMA1, a highly expressed protein in metastasizing melanoma, prostate cancer, and glioma[31]. Another research study resulted in a similar but more interesting conclusion. MiR-211 is encoded within the sixth intron of TRPM1, which is known as melastatin and is greatly down-regulated in metastatic melanomas; it is widely believed to function as a melanoma tumor suppressor. Levy et al. reported that the tumor suppressive activity of TRPM1 in melanoma is not mediated by this gene itself but instead by miR-211 hosted within an intron of TRPM1 because of the increasing expression of miR-211 but not a TRPM1 reduced migration and invasion of invasive human melanomas cells. This result implicates miR-211 as a suppressor of melanoma invasion whose expression is silenced or selected against via the suppression of the entire TRPM1 locus during human melanoma progression. Additionally, they also identified three central node genes, IGF2R, TGFBR2, and NFAT5, as the target of miR-211[32]. Notably, the micropthalmia-associated transcription factor (MITF), which is important for

melanocyte development and function, is needed for high TRPM1 expression[31], and thus, MITF contributes to miR-211 expression, suggesting that the tumor-suppressor activities of MITF may at least be partially executed through miR-211's tumor suppressing effect.

MiR-196a is another documented tumor suppressor in melanoma by Dr.Bosserhoff's group [33, 34]. First, they found that miR-196a was significantly down-regulated in malignant melanoma cell lines and tissue samples when screening differential miRNAs. Re-expressing miR-196a *in vitro* can dramatically reduce the invasive behavior of melanoma cells, which is partially believed to account for the negative regulating expression of the transcription factor HOX-C8, which is a member belonging to the homeobox genes family. By investigating a potential "miR-196a → HOX-C8 → target gene" model, they further identified cadherin-11, calponin-1, and osteopontin as the downstream targets of miR-196a[34]. Additionally, they elucidated that down-regulated miR-196a in melanoma cells leads to enhanced HOX-B7 mRNA and protein levels, another member of the homeobox genes family, which subsequently raise Ets-1 activity, another transcription factor, by inducing basic fibroblast growth factor (bFGF). Ets-1 eventually up-regulates bone morphogenetic protein 4 (BMP-4) playing an important role in melanoma progression[33].

Chen et al. reported that the over-expression of miR-193b in melanoma cell lines repressed cell proliferation by down-regulating cyclin D1 (CCND1). They identified 31 miRNAs that are differentially expressed (13 up-regulated and 18 down-regulated) in metastatic melanomas relative to benign nevi by profile-analyzing tissue samples from benign nevi and metastatic melanomas. Notably, miR-193b was significantly down-regulated in the melanoma tissues examined. Functional studies revealed miR-193b is a tumor suppressor in melanoma. Their study indicates that miR-193b is able to repress cell proliferation and regulate CCND1 expression, suggesting that the deregulation of miR-193b may play an important role in melanoma development[35].

4. Molecular mechanism of microRNA associated with melanoma

The development of rational treatments for melanoma will depend on our taking advantage of its clinical features' molecular basis. The necessary understanding of the molecular genetics underlying melanoma is gradually emerging[36]. Many key genes and signaling pathways have been characterized for their functions associated with melanoma. For example, the micropthalmia-associated transcription factor (MITF) is one of the most recognizable oncogenes in melanoma, which regulates cell proliferation and apoptosis, and is over-expressed in 10-20% of human melanoma[32]. Also, it is a member in Myc supergene family of basic helix-loop-leucine-zipper transcription factors, which are necessary for functional melanocyte formation[37]. Because MITF's critical role in melanoma progression, several recent studies have explored miRNAs' impact on melanoma through MITF mediated pathways.

4.1 MicroRNAs targeting MITF

MicroRNA.org, an online database for miRNA targets prediction, provides more than 300 miRNA candidates that putatively target MITF. However, only few of them have been verified.

MiR-137 is located in the chromosomal region, 1p22, which is known to harbor an allele for melanoma susceptibility. The bioinformatics and *in vitro* analyses verified that miR-137 had targeted MITF in melanoma cells[20]. Most recently, Chen et al. reported the down-regulation of MITF by miR-137 in uveal melanoma cells[38]. Additionally, the over-expression of miR-137

in uveal melanoma cells can lead to a significant decrease in cell growth through inducing G1 cell cycle arrest, which might be due to its suppression on oncogenic tyrosine kinase protein receptor c-Met, cell cycle-related protein CDK6, and MITF[38].

Segura et al. described miR-182 also as a negative regulator of MITF expression[25]. MiR-182 is located in 7q31-34, a chromosomal region frequently altered in melanoma. MiR-182 was demonstrated to increase the invasive potentials of melanoma cells by repressing MITF and FOXO3, a Forkhead family transcription factor. Importantly, 7q31-34 also harbors c-Met (encodes hepatocyte growth factor receptor with tyrosine-kinase activity) and BRAF (member of the raf/mil family of serine/threonine protein kinases), two important regulators in the MAPK/ERK signaling pathway[39]. They found that miR-182 was over-expressed not only in human melanoma cell lines but also in tissue specimens. These results were inversely correlated with MITF and FOXO3 expression in the prediction of melanoma progression and development. Moreover, miR-182 ectopic expression in melanoma cells stimulated the anchorage-independent growth and invasion using an *in vitro* extracellular matrix assay, and promoted melanoma lung metastasis in a mouse model, whereas miR-182 down-regulation impeded invasion and triggered apoptosis of melanoma cells.

MiR-340 is capable of causing mRNA degradation by interacting with its 3'-UTR of MTIF. Interestingly, the RNA-binding protein coding region determinant-binding protein (CRD-BP) is highly expressed in melanoma and can directly bind the 3'-UTR of MITF mRNA thus preventing miR-340 access, resulting in the stabilization of the MITF transcript and the elevation the transcription of MITF[40].

4.2 MiRNAs regulated by MITF in transcription

As described earlier, miRNA has a similar transcription and regulatory process to other RNA molecules. MITF has been demonstrated as a transcriptional factor[37]. Ozsolak et al. identified a number of miRNAs that were regulated by MITF in melanoma cells using nucleosome mapping and linker sequence analyses[41]. These miRNAs included some members of let-7 family (let-7a-1, -7d, -7f-1 and -7i), miR-221/222, miR-17-92 cluster, miR-106-363 cluster, miR-29, miR-146a, miR-148b and miR-125b[41]. A few of them, such as let-7, miR-17-92, miR-221/222, and miR-148, have been documented for their abilities to connect many key genes and to signal pathways to melanoma. Here, we will illustrate a MITF-centered regulatory loop with the involvement of multiple miRNAs/mRNAs/pathways (Figure 3).

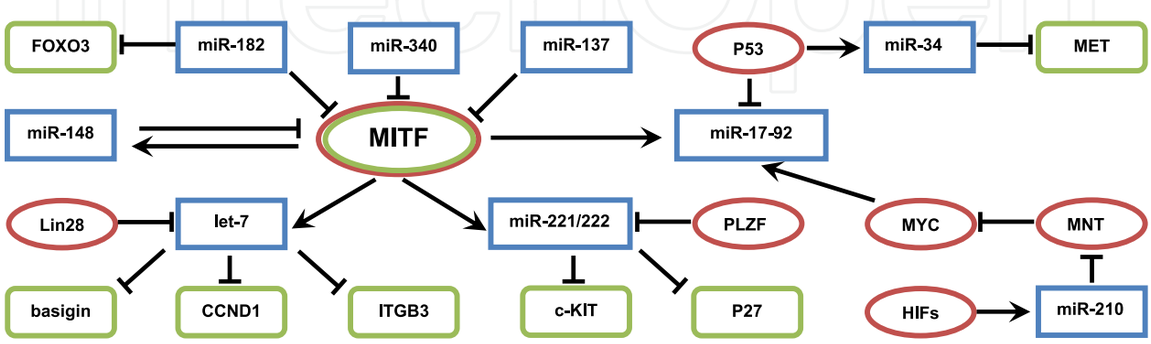

Fig. 3. Molecular mechanism of microRNA regulation in melanoma miRNA target gene transcription factor

The Let-7 family is highly conserved across species in sequence and function, which were first validated to be involved in tumorigenesis[42]. Schultz et al. revealed five members of the let-7 family (let-7a, -7b, -7d, -7e, and -7g) as being significantly down-regulated in primary melanoma when compared with benign nevi, which suggested that the let-7 family might be tumor suppressors in melanoma[43]. The ectopic over-expression of let-7b diminished the anchorage-independent growth ability of melanoma cells and inhibited the cell-cycle progression. The over-expression of let-7b eventually repressed cyclins (D1, D3 and A) and cyclin-dependent kinase (CDK4) all of which had been described to play a role in melanoma development. Most recently, another study showed that the over-expression of let-7b in the melanoma cell line B16-F10 exhibited an inhibition of both cellular proliferation and colony formation. Let-7b can reduce lung metastasis by repressing the expression of basigin, which is a stimulator for tumor cells producing matrix metalloproteinases (mmps) and is highly expressed on the surface of tumor cells[44].

Let-7a is considered lost in melanoma when one is comparing primary melanocytes to malignant melanoma cell lines. Sequencing analysis suggested Let-7a had an interaction with the 3'UTR of integrin β3 mRNA[26]. Integrin β3 is highly related to melanoma progression and leads to an enhanced migratory and an enhanced invasive potential of melanoma cells[45]. The transfection of melanoma cells with let-7a pre-miR molecules resulted in the down-regulation of integrin β3 mRNA and protein expression, which suggested that the loss of let-7a expression might be one of the essential regulatory mechanisms leading to an increase integrin β3 expression in melanoma cells[26]. Muller et al. also proved that the over-expression of let-7a in melanoma cells reduced their invasive potential by approximately 75%; meanwhile transfection with let-7a anti-miRs and anti-sense oligonucleotides that directly binds and inhibits the actions of miRNAs, resulted in the induction of the integrin β3 expression and induced the migration of anti-let-7a-transfected melanocytes. These findings revealed let-7a to be an important integrin β3 regulator, and the loss of let-7a is thus involved in the development and progression of malignant melanoma.

The miR-17-92 cluster locates to chromosome 13 and contains 6 members (miR-17, -18a, -19a, -20a, -19b-1 and -92a-1), while another miRNA cluster, miR-106-363that shares many similarities with the miR-17-92 cluster locates to the X chromosome; it also consists of 6 members (miR-106a, -18b, -20b, -19b-2, -92a-2 and -363). Both miRNA clusters are described as being oncogenic and found to be highly expressed in a variety of cancers[46, 47]. Muller et al. compared the miRnomes of normal human melanocytes and well characterized melanoma cell lines derived from primary tumors and melanoma metastases and showed that all members of the miR-17-92 cluster were up-regulated in primary tumor cell lines compared with normal melanocytes. The expression of the miR-17-92 cluster was even higher in metastatic cell lines with an approximately two-fold up-regulation as compared to primary melanoma cell lines. The expression of the miR-106-363 cluster was similar to the expression of the miR-17-92 cluster in melanocytes and melanoma cells. They detected a strong up-regulation of miR-106a expression in primary tumor cells and a further increase in expression levels in metastatic melanoma cells[48]. In addition to finding miR-17-5p, miR-18a, miR-20a, and miR-92a over-expressed and miR-146a, miR-146b, and miR-155 down-regulated in the majority of melanoma cell lines with respect to melanocytes, Levati et al. found that ectopic expression of miR-155 in melanoma cells inhibits the proliferation[49]. These results imply that the miR-17-92 cluster would be involved in melanoma progression.

Both miR-221 and miR-222 are regulated by MITF at the transcription level[21]. These two miRNAs are clustered on the X chromosome, are transcribed as a common precursor, and

are over-expressed in a variety of cancers with the function of repressing the c-Kit receptor. In normal melanocytes, stem cell factor (SCF)-dependent c-Kit-mediated signaling supports proliferation, migration, and differentiation of cells[50]. Constitutive activation of c-Kit receptor tyrosine kinase (RTK) alone does not induce a tumorigenic transformation of the melanocytes in neither *in vitro* nor *in vivo*[51]; however, cutaneous melanoma are often characterized with a loss of c-Kit expression[52]. The inhibition of c-Kit RTK in c-Kit-positive melanoma showed an increased apoptosis and G1 phase cell-cycle arrest[52], while the re-expression of c-Kit in the c-Kit-negative melanoma cells restored c-Kit-mediated apoptosis and resulted in a loss of tumorigenic potential[53]. In accordance with these observations, Felicetti et al. found that up-regulated miR-221/222 repressed the expression of the c-Kit receptor and p27Kip1 (cyclin-dependent kinase inhibitor 1B, CDKN1B) tumor suppressor during melanoma progression from a weakly invasive primary tumor to a more invasive phenotype[21]. The over-expression of miR-221/222 in melanoma cells led to an increase in their proliferation and invasion *in vitro* and accelerated tumor growth in a mouse melanoma model. Conversely, treatment with anti-miRs against both miRNAs resulted in a reduced proliferation rate and migration of melanoma cells with a high level of miR-221/222 abilities. They also found that the elevated expression of miR-221/222 in melanoma cells was caused by the loss of a transcription factor, promyelocytic leukemia zinc finger (PLZF). PLZF binds to the miR-221/222 promoter and inhibits their transcription in normal melanocytes.

Cyclin-dependent kinase 2 (CDK2) has been reported to phosphorylate PLZF, triggering its ubiquitination and subsequent degradation[54]. Furthermore, p27Kip1 is important for the efficient induction of G1 cell-cycle arrest by PTEN and is necessary for PTEN-induced down-regulation of CDK2 [55, 56]. Additionally, PTEN is an inhibitor for Ha-ras-mediated astrocyte elevated gene-1 (AEG-1) transactivation [57]. AEG-1 directly binds PLZF, preventing it from binding its target promoters[58], including those of miR-221/222. Therefore, PTEN may be an important negative regulator of miR-221/222 in melanoma as it is capable to maintain PLZF levels to bind the miR-221/222 promoters, preventing their transcription. Although there are no miRNAs currently described to target PTEN in melanoma, recent reports highlighted miR-221/222 in aggressive non-small cell lung cancer (NSCLC) and hepatocarcinoma as oncomirs capable of directly targeting and inhibiting the expression of the tumor suppressor, PTEN [59, 60]. As a result, there may be a positive feedback loop for miR-221/222 expression, promoting melanoma progression through the joint inhibition of PTEN and p27Kip1 and blocking PTEN/AEG-1/PLZF and/or p27Kip1/CDK2/PLZF-mediated repression of miR-221/222.

Additionally, Igoucheva et al. confirmed that c-Kit was down-regulated by miR-221/222 and revealed that c-Kit regulation was mainly based on miRNA-dependent post-transcriptional mechanisms instead of an AP-2-dependent transcriptional mechanism[50]. Recently, mutations have been identified in both miRNAs and target genes that disrupt regulatory relationships. Godshalk et al. described a genetic variant in the 3' UTR of the KIT; this KIT variant results in a mismatch in the seed region of a miR-221 complementary site and thus leads to an increased expression of the KIT oncogene [61].

Haflidadóttir et al. suggested that miR-148 affects MITF mRNA expression in melanoma cells through a conserved binding site in the 3'UTR sequence of mouse and human MITF[37]. Interestingly, it seemed that MITF transcriptionally regulated the expression of miR-148b in melanoma cells[41], which showed that there was a negative feedback regulation between miR-148 and MITF to control their balance.

5. Clinical applications of miRNA in melanoma

5.1 Diagnostic miRNAs

Several years ago, we and other groups independently demonstrated that miRNAs were relatively more stable and tolerate RNAases better than mRNAs in both archived tissue samples and in blood samples[27, 41, 62], which suggests that miRNAs have the potential to be valuable, practical, and reliable biomarkers for disease states.

Recently, several groups employed a high through-put microarray technique to discover miRNA biomarkers from formalin-fixed and paraffin-embedded (FFPE) melanoma samples[9, 63, 64]. A number of miRNAs have shown the potential to become diagnostic markers for melanoma based on data from clinical samples and array analysis[9, 63, 64].Radhakrishnan et al. examined the presence of oncogenic miRNA (oncomirs) in uveal melanoma using FFPE specimens by comparing miRNA expression profiles between non-invasive tumor and melanoma metastatic to the liver. They revealed 19 miRNAs that were expressed in non-metastatic melanoma but were absent in metastatic melanoma, and they revealed 11 miRNAs with the opposite expression pattern[65].

In addition to FFPE samples, blood samples have been used to identify the melanoma tumor biomarkers[66]. Leidinger et al screened almost 900 human miRNAs, 55 blood samples, including 20 samples of healthy individuals, 24 samples of melanoma patients as test set, and 11 samples of melanoma patients as independent validation set. They identified 51 altered miRNAs (21 down-regulated miRNAs and 30 up-regulated miRNAs) that can potentially distinguish melanoma patients from healthy controls. More excitingly, the panel consisting of 16 deregulated miRNAs can reach a classification accuracy of 97.4%, a specificity of 95%, and a sensitivity of 98.9%. Therefore, this study again demonstrates that signatures of miRNA expression can act as useful biomarkers for melanoma[66]

Kanemaru et al, in particular, indentified the serum level of miR-221 as a new tumor marker in patients with malignant melanoma[67]. MiR-221 is usually up-regulated in malignant melanoma cells as we discussed earlier. By measuring the miR-221 levels in serum from 94 malignant melanoma patients and 20 healthy controls, they found that the circulating miR-221 was detectable and could be quantified in serum samples; the serum levels of miR-221 were significantly increased in malignant melanoma patients when compared to healthy controls. Among the malignant melanoma patients, the miR-221 levels were significantly increased in patients with advanced melanoma compared to those with melanoma in situ, and the levels were correlated with tumor thickness. Moreover, they also revealed a decreasing tendency for the miR-221 levels along with the surgical removal of the primary tumor, but miR-221 was found to increase again at recurrence, which strongly suggested that circulating miR-221 may be useful not only for diagnosing malignant melanoma and for differentiating melanoma with different stages, but it could also be useful as a prognostic marker for patients with malignant melanoma[67].

5.2 Prognostic miRNAs

Like miR-221, some other miRNAs have been reported for their prognostic signatures in melanoma. Worley et al. were the first to use a genome-wide, microarray-based approach to investigate the value of miRNA expression patterns in predicting metastatic risk in uveal melanoma. They found the most significant discriminator to classify low and high metastatic risk was let-7b and miR-199a expression. A classifier system that included the top six miRNA discriminators accurately distinguished melanoma patient tissues with high

metastatic propensity with 100% sensitivity and specificity[23]. Satzger et al. found that miR-15b and miR-210 were significantly up-regulated in parallel with the down-regulation of miR-34a in melanoma compared to nevi. These three miRNAs were then analyzed in 128 primary melanoma patients, including detailed clinical follow-up information; only the high expression of miR-15b was significantly correlated with the poor recurrence-free survival and overall survival by the univariate Kaplan-Meier and the multivariate Cox analyses. Furthermore, the transfection of anti-miR-15b into melanoma cells led to a reduced tumor cell proliferation and an increased apoptosis. Their results showed that miR-15b might be a novel melanoma biomarker contributing to poor prognosis and tumorigenesis[68]. Segura et al. identified the signature of a panel of miRNAs for predicting post-recurrence survival in metastatic melanoma by analyzing 59 formalin-fixed paraffin-embedded melanoma metastasis samples. Eighteen over-expressed miRNAs are significantly correlated with longer survival (>18 months). The signature of a six-miRNA panel (miR-150, miR342-3p, miR-455-3p, miR-145, miR-155, and miR-497) can have a better advantage to classify stage III patients into different prognostic categories because it is an independent predictor of survival[69]. Additionally, the down-regulation of miR-191 and the up-regulation of miR-193b were reported to be associated with poor melanoma-specific survival[70].

5.3 Therapeutic miRNAs

Since miRNAs are critical in regulating many cellular events and are highly deregulated in various cancers, including melanoma, it is likely that miRNAs could be effective targets for treatment. The basic strategies of miRNA-based therapeutics are: first, delivering highly expressed miRNAs that are tolerated in normal tissues but are lost in diseased cells , which may provide a general strategy for miRNA replacement therapies[71]; and second, using specific compounds targets aberrant oncogenic miRNAs, especially for over-expressed miRNAs.

Sun et al. recently found that genistein, an isoflavone isolated from soybeans, inhibited human uveal melanoma cells growth in vitro and in vivo and altered the expression of miR-27a and its target gene zinc finger and BTB domain containing 10 (ZBTB10), hinting at the contributions of miR-27a to genistein's inhibitory effect on melanoma growth[72]. Das et al. found that human polynucleotide phosphorylase (hPNPase(old-35)), a type I IFN-inducible 3'-5' exoribonuclease, can specifically down-regulate the expression of miR-221, a regulator of p27(kip1) and usually over-expressed in melanoma, as stated previously. This study implied that targeting over-expression of hPNPase(old-35) might provide an effective therapeutic strategy for miR-221-overexpressing and IFN-resistant tumors, such as melanoma[73]. MiR-137 acted as a tumor suppressor and usually decreased in uveal melanoma as previously described. Chen et al described one avenue to increase the expression levels of miR-137 through treatment with a DNA hypomethylating agent, 5-aza-2'-deoxycytidine, or a histone deacetylase inhibitor, trichostatin A, for down-regulating its cognate target genes MITF and CDK6[38]. MiR-182 is a pro-metastatic miRNA frequently over-expressed in melanoma. Huynh et al. assessed the effect of anti-miR-182 oligonucleotides in a mouse model with melanoma liver metastasis and confirmed that miR-182 levels were effectively down-regulated in the tumors of anti-miR-treated mice. This study implies that anti-miR may be a promising therapeutic strategy for metastatic melanoma[74]. Targeted delivery of RNA-based therapeutics for cancer therapy remains a challenge. By developing an improved liposome-polycation-hyaluronic acid (LPH) nanoparticle vehicle, Chen et al. reported that miR-34a was successfully delivered to B16-F10 melanoma lung metastasis-bearing mice, and it could specifically suppress the surviving expression in the metastatic tumor and reduced tumor load in the lung[75].

Progression		miRNA	Target(s)	Regulatory Factor	Associations
Melanocyte ↓ Primary Melanoma	↓	let-7a	ITGB3	Promoter methylation	↓ Migration, invasion
		let-7b	CCND1		↓ Proliferation, differentiation
		miR-137	MITF		↓ Cell migration, invasion and survival
		miR-155			↑ Proliferation
		miR-324-5p			
		miR-34a	MET		↓Proliferation
		miR-106a			
		miR-126			
		miR-133a			
		miR-141			
	↑	miR-145			
		miR-15b			↑ Proliferation, survival
		miR-200c			Migration style transition
		miR-27b			
		miR-210	MNT		↑ Proliferation
Primary Melanoma ↓ Metastasis	↓	miR-126			
		miR-200c			
		miR-141			
		miR-133a			
		miR-34a			
		miR-199a*	c-Met		↓ Cell migration, invasion and survival
		miR-34b/c	c-Met		↓ Cell migration, invasion and survival
		miR-106a			
		miR-133a			
	↑	miR-199a*			
		miR-182	MITF, FOXO3		↑ Migration, invasion and survival
		let-7b			
Melanocyte ↓ Metastasis	↓	miR-133a			
		miR-155			↓ Proliferation, survival
		miR-193b			
		miR-196a	HOX-C8 HOX-B7		↓Invasion
		miR-133a			
		miR-17-5p			
		miR-18a			
		miR-19a/b			
	↑	miR-221/222	c-Kit, p27	PLZF	↑ Proliferation, invasion; ↓ differentiation
		miR-532-5p	RUNX3		↑Invasion
		miR-20a			
		miR-92a			

Table 1. MicroRNAs in melanoma progression

6. Summary

There were approximately 40 publications from the past year and a half that reported the involvement of miRNA in melanoma research from both laboratory and clinical settings, which evidences the perspective of miRNA as one of the most valuable biomarkers and therapeutic targets in current melanoma research. We are pleased to find the that research trend of miRNA and melanoma has changed from solely searching altered specific miRNAs to exploring molecular networks and connections between miRNAs and signaling pathways involved in the progression of melanoma (Table 1). Certainly, a better understanding of the biological machinery of miRNA function will allow us to visibly observe the genetic impacts on carcinogenesis and to explore effective therapeutic strategies for conquering melanoma in the near future.

7. Acknowledgement

We specifically acknowledge the Ochsner Journal for giving us a permission to represent partial contents from our pervious publication "MicroRNA in melanoma". We also appreciate Ms. Amy Brown for her editorial assistance.

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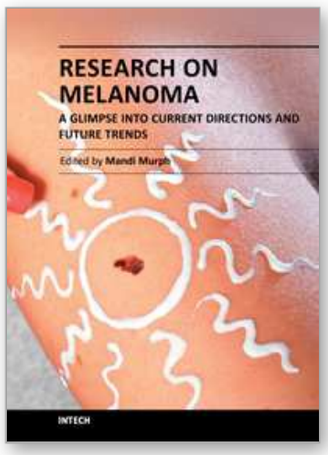

Research on Melanoma - A Glimpse into Current Directions and Future Trends

Edited by Prof. Mandi Murph

ISBN 978-953-307-293-7
Hard cover, 414 pages
Publisher InTech
Published online 12, September, 2011
Published in print edition September, 2011

The book Research on Melanoma: A Glimpse into Current Directions and Future Trends, is divided into sections to represent the most cutting-edge topics in melanoma from around the world. The emerging epigenetics of disease, novel therapeutics under development and the molecular signaling aberrations are explained in detail. Since there are a number of areas in which unknowns exist surrounding the complex development of melanoma and its response to therapy, this book illuminates and comprehensively discusses such aspects. It is relevant for teaching the novice researcher who wants to initiate projects in melanoma and the more senior researcher seeking to polish their existing knowledge in this area. Many chapters include visuals and illustrations designed to easily guide the reader through the ideas presented.

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Xiaobo Li and Yaguang Xi (2011). Predictive Capacity and Functional Significance of MicroRNA in Human Melanoma, Research on Melanoma - A Glimpse into Current Directions and Future Trends, Prof. Mandi Murph (Ed.), ISBN: 978-953-307-293-7, InTech, Available from: http://www.intechopen.com/books/research-on-melanoma-a-glimpse-into-current-directions-and-future-trends/predictive-capacity-and-functional-significance-of-microrna-in-human-melanoma

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