miRNAs in Cancer

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Scientific investigations have shown the involvement of microRNAs (miRNAs) as a new key factor for cancer development and progression. Owing to their role in the regulation of gene expression and their stability (resistance to endogenous RNase activity) in body fluids, miRNAs have been extensively shown to be of particular interest for diagnosis, recurrence, identification, and treatment of cancer metastasis.

Despite miRNAs being considered small conserved regulators with the limitation of target specificity, we outline the dual role of melanoma-associated miRNAs, as oncogenic and/or tumor suppressive factors, compared to other tumors.

Keywords: melanoma ; oncomiRNAs ; tumor suppressor miRNAs

1. Introduction

It has been widely demonstrated that miRNAs are able to modulate the expression of multiple targets, some of which play oncogenic or tumor-suppressive roles.

2. The Dual Role of miRNAs in Cancer

Evidence suggests that some miRNAs can also have opposite effects in different tumoral contexts, as listed in Table 1.

Table 1. The most representative miRNAs with an opposite role in melanoma and other tumors.

miRNA	References
miR-9	[1][2]
miR-21	[3][4]
MiR-30b	[5][6][7]
MiR-30d	[5][6][7][8]
miR-125b	[9][10]
miR-155	[11][12][13]
miR-146a	[14][15]
miR-205-5p	[16][17][18][19][20]
miR-211	[21]
miR-224 5p	[22][23][24]

miR-452	[25][23][26]
miR-542-3p	[27][28][29]

Notably, the dual role of miRs and the melanoma system has been established, as summarized in Table 1. For instance, among the tumor suppressors, Skouti et al. showed miR-205-5p gradually decreased during melanomagenesis in mice and was able to reduce cell and proliferation, and delay tumor initiation [16].

Several studies have focused on miR-205-5p and its dual role in cancer. It has been reported as oncomiR in lung and nasopharyngeal cancers by targeting PTEN [17][18][30]. Furthermore, a tumor suppressor role has also been described in prostate [19], breast [20], melanoma [31], glioblastoma [32], and colon cancers [33] by targeting c-MYC [34], PKCε [19], and VEGF-A [32]. Further, miR-9 has been found to be downregulated in metastatic melanomas compared to primary tumors. It has been shown to be able to downregulate SNAIL1 and consequently promote CDH1 expression, inhibiting melanoma cells' ability to invade [35] while miR-9 has been described either as an oncomiR or tumor suppressor in a variety of other cancers [2].

MiR-21 negatively regulates MKK3 and acts as a tumor suppressor in melanoma by inhibiting cell growth and metastasis [3]. Instead, miR-21 inhibits tumor apoptosis and promotes proliferation and metastasis by downregulating p53 expression in uveal melanoma cell lines [4]. miR-125b represents another example of a miRNA able to act as either an oncomiR or a tumor suppressor, depending on the context. It acts as an oncomiR in the vast majority of hematologic malignancies but as a tumor suppressor in many solid tumors. This apparent paradox can be explained by considering the fact that a single miR-125b targets antiapoptotic factors (MCL1, BCL2L2, and BCL2), proapoptotic factors (TP53, BAK1, BMF, BBC3, and MAPK14), proproliferative factors (JUN, STAT3, E2F3, IL6R, and ERBB2/3), metastasis promoters (MMP13, LIN28B, and ARID3B), and metastasis inhibitors.

MiR-125b has been found to be upregulated in some tumor types, e.g., colon cancer and hematopoietic tumors, where it displays an oncogenic potential, by inducing cell growth and proliferation and blocking apoptosis. In contrast, it acts in other tumor entities, e.g., melanoma, as a tumor suppressor by targeting c-Jun [9][10].

Indeed, miR-155 shows a dual role in various types of cancer cells, such as melanoma. Although miR-155 has been described as an oncogene in various type of cancers, Levati and colleagues demonstrated that miR-155 is able to inhibit the proliferation of melanoma cell lines by targeting the oncongene SKI [11]. Similarly, Li and colleagues and Qin and colleagues demonstrated that miR-155 exerts a tumor-suppressive effect in gastric cancer and ovarian cancer-initiating cells by targeting SMAD2 and CLDN1, respectively [13]. Another excellent example of the opposite roles is provided by miR-30d and miR-30b-5p, which are associated with progression from primary to metastatic melanoma [36].

MiR-30d acts as a tumor suppressor in prostate cancer cell proliferation and migration by targeting NT5E and is regulated by the Akt/FOXO pathway in renal cell carcinoma [7][8]. MiR-30b-5p acts as a tumor suppressor microRNA in esophageal squamous cell carcinoma [5]. MiR-30b suppresses tumor migration and invasion by targeting EIF5A2 expression in gastric cancer cells [6].

Furthermore, miR-146a has been shown to play a dual role in malignancy. MiR-146a has been identified as being able to promote the tumor growth of malignant melanoma and, at the same time, to impair tumor cell dissemination. High levels of miR-146a expression during melanoma progression triggers tumor growth through inhibition of lunatic fringe (LFNG) and NUMB and activation of the NOTCH/PTEN/AKT pathway. In contrast its downregulation in circulating tumor cells (CTCs) suppresses tumor dissemination through modulation of the expression of ITGAV and ROCK1 [14][15].

It has been shown that miR-211 exhibited a dual role in melanoma progression, promoting cell proliferation while inhibiting metastatic spread in a xenograft mice model [21].

High expression levels of miR-224-5p have been detected in a large variety of tumors, such as glioma, colorectal cancer, and renal carcinoma, and is downregulated in uveal melanoma. Notably, Li et al. showed that miR-224-5p is involved in the proliferation, invasion, and migration of uveal melanoma (UM) cells via regulation of the expression of PIK3R3 and AKT3 [22]. Results from Gan et al. highlighted the correlation of the downregulated expression of miR-224-5p with the clinical progression and prognosis of prostate cancer [24]. Knoll et al. showed that the miR-224/miR-452 cluster is significantly increased in advanced melanoma and that ectopic expression of miR-224/miR-452 induces EMT and cytoskeletal rearrangements, and enhances migration/invasion. Conversely, miR-224/miR-452 depletion in metastatic cells induces the reversal of EMT, inhibition of motility, loss of the invasive phenotype, and an absence of lung metastases in mice.

It has been shown that miR-224/miR-452 targets the metastasis suppressor TXNIP and induces feedback inhibition of E2F1. MiR-224/452-mediated downregulation of TXNIP is essential for E2F1-induced EMT and invasion [37]. Also, the tumor-suppressive role of miR-452 has been reported in gliomas, targeting stemness regulators, such as BMI-1 [34].

The Rang group's results collectively indicated that miR-542-3p acts as a metastasis suppressor in melanoma [27] and as a tumor suppressor in ovarian cancer by directly targeting CDK14) and promoting the proliferation of osteosarcoma cells in vitro [38][39][40]. Furthermore, Haflidadóttir et al. reported miR148's dual/opposite role in MITF regulation [41].

This set of observations highlights the polyvalence of miRNAs as an oncogenic or tumor suppressor, even within a single cancer type.

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