Cancer Gene Therapy (2016) 00, 1–2

www.nature.com/cgt

SHORT COMMUNICATION

Circulating microRNA: a new candidate for diagnostic biomarker in neuroblastoma

M Mohammadi[1], M Goodarzi[2], MR Jaafari[3], HR Mirzaei[4] and H Mirzaei[5]

Neuroblastoma (NB) is known as a pediatric neoplasm that is associated with variable histopathological features. The use of biomarkers contributes to the monitoring and treatment of various malignancies such as NB. The identification of novel biomarkers such as (epi)genetic biomarkers and microRNAs (miRNAs) in NB has led to better treatments of NB. Among them, miRNAs have emerged as powerful tools in diagnosis, prognosis and therapeutic biomarkers for patients with NB. Circulating biomarkers such as circulating miRNAs present in body fluids (for example, plasma, serum and urine) provided an interesting field of study in NB treatment. The miRNAs have central roles in different pathogenic events in various malignancies such as NB. Hence, these molecules can be a suitable candidate for monitoring and treating NB patients. Here, we summarize some miRNAs as potential prognosis, diagnosis and therapeutic biomarkers in NB.

Cancer Gene Therapy advance online publication, 14 October 2016; doi:10.1038/cgt.2016.45

miRNAs AND NEUROBLASTOMA

The neuroblastoma (NB) is known to be an embryonal tumor of the nervous system. This disease occurs in children and young people; the median age at diagnosis is 17 months.[1,2] The backbone of therapy approaches encompasses surgical resection, radiotherapy and immunotherapy.[2] However, NB is considered heterogeneous. Several studies revealed that some genes and molecules are involved in the progression of NB.[2] These factors such as age, alteration of genes expression and different miRNAs can affect the development of this disease.[2] Various signaling pathways have significant roles in different stages of NB. The central role of PI3K-Akt-PTEN and RAF-MEK-ERK as molecular targets is to regulate and control downstream agents and effectors of coordinated apoptosis, cell division, angiogenesis, tumor growth, invasion and cellular metabolism in NB.[2] miRNAs are a class of small noncoding RNAs with a length of ~21–25 nucleotides, which regulate gene expression posttranscriptionally by binding to the 3′ untranslated region of their mRNA targets, resulting in degradation or transcriptional repression of the targeted mRNA.[3–5] miRNAs control numerous cellular/molecular processes such as apoptosis, cell proliferation and differentiation.[6,7] Deregulated expression of miRNAs contributes to the initiation or development of numerous diseases such as cancer. Several studies revealed that some biomarkers such as miRNAs have significant roles in pathogenesis of NB. These molecules enable the regulation of various pathways such as Wnt, epithelial-mesenchymal transition and apoptosis pathways. Figure 1 illustrates various pathways involving miRNAs in NB.

CIRCULATING miRNAs AND NB

The majority of NB patients have been diagnosed at advanced stages of this disease. Hence, fast and easy detection in NB patients can contribute to diagnosis and monitoring responses to therapy in these patients.[2,8] With improved detection methods, the identification of powerful biomarkers can increase survival and response to different drugs. Circulating biomarkers present in body fluids such as serum, plasma and urine are known as powerful tools in diagnosis, prognosis and therapy in several solid tumors such as NB.[9,10] These biomarkers have a lot of advantages such as allowing noninvasive, easy and fast detection.[6] Some studies revealed that there are several circulating biomarkers in NB, one of them being circulating miRNA.[9] On the other hand, others demonstrated that circulating miRNAs are involved in various pathogenesis pathways.[4] miRNAs have significant biological roles in signaling pathways, and may induce or inhibit progression of various cancers such as NB.[6,9] Ramraj *et al.*[9] have assessed miRNAs present in serum that are involved in aggressive NB based on the non-metastatic mouse models. Their result indicated that 33 out of 42 miRNAs showed a significant upregulation (more than twofold) in animals with high-risk NB. Preferential exclusion of mouse miRNA with sequence homology blast indicated 11 (out of 33 upregulation) unique human miRNAs.[9] Consistently, homology blasting identified 13 (out of 42 downregulation) miRNAs. Table 1 shows various circulating miRNAs that can be used as prognosis, diagnosis and therapeutic biomarkers.

CONCLUSION

NB is known as a heterogenetic disease in children. Despite obtaining many achievements in the finding and understanding of molecular pathways and biological heterogeneity of this disease, it remains a main malignancy in children. Therefore, the recognition of new biomarkers that are associated with prognosis, diagnosis, therapy, survival, response to treatment and relapse

[1]Hepatitis Research Center and Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, Lorestan University of Medical Sciences, Khorramabad, Iran; [2]Department of Biosystems, Faculty of Bioscience Engineering, Katholieke Universiteit Leuven—KU Leuven, Heverlee, Belgium; [3]Biotechnology Research Center, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran; [4]Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran and [5]Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Correspondence: Dr HR Mirzaei, Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran 1417613151, Iran or Dr H Mirzaei, Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad 9177948564, Iran.
E-mail: h-mirzaei@razi.tums.ac.ir or h.mirzei2002@gmail.com
Received 23 May 2016; revised 6 June 2016; accepted 9 June 2016

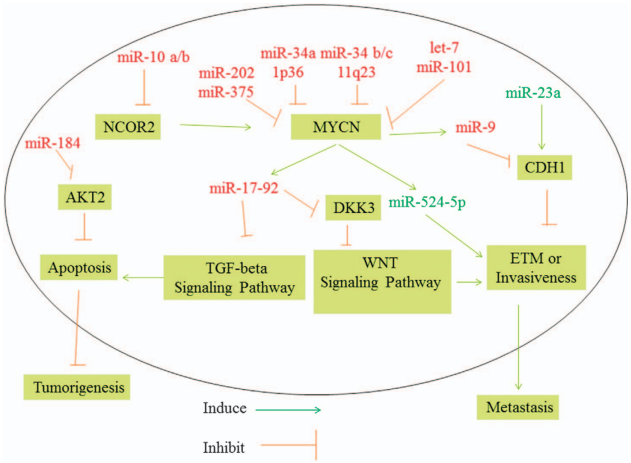

Figure 1. Schematic diagram of various miRNAs network in NB tumorigenesis and metastasis. ETM, epithelial-mesenchymal transition; miRNA, microRNA; NB, neuroblastoma; TGF, transforming growth factor.

after treatment with various drugs can contribute to improve and monitor the state of the disease in NB patients. The identification of novel biomarkers such as genetic, epigenetic, enzymes and circulating biomarkers can open new insights in NB therapy. Among the present biomarkers, circulating miRNAs have emerged as potential candidates in prognosis and diagnosis of patients with NB. These molecules have key roles in various events at different stages of NB. Thus, these molecules can be used as a powerful tool for monitoring and treating NB patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Table 1. Various circulating miRNAs in NB

Biomarker	*Expression in NB*	*Sample*	*Reference*
miR-1206	Downregulated	*In vivo*/serum	9
miR-548a-5p	Downregulated	*In vivo*/serum	9
miR-548f	Downregulated	*In vivo*/serum	9
miR-639	Downregulated	*In vivo*/serum	9
miR-640	Downregulated	*In vivo*/serum	9
miR-641	Downregulated	*In vivo*/serum	9
miR-647	Downregulated	*In vivo*/serum	9
miR-662	Downregulated	*In vivo*/serum	9
miR-886-3p	Downregulated	*In vivo*/serum	9
miR-887	Downregulated	*In vivo*/serum	9
miR-888	Downregulated	*In vivo*/serum	9
miR-576-5p	Downregulated	*In vivo*/serum	9
miR-600	Downregulated	*In vivo*/serum	9
miR-513a-5p	Upregulated	*In vivo*/serum	9
miR-198	Upregulated	*In vivo*/serum	9
miR-1280	Upregulated	*In vivo*/serum	9
miR-1304	Upregulated	*In vivo*/serum	9
miR-1308	Upregulated	*In vivo*/serum	9
miR-1908	Upregulated	*In vivo*/serum	9
miR-513b	Upregulated	*In vivo*/serum	9
miR-548 f	Upregulated	*In vivo*/serum	9
miR-580	Upregulated	*In vivo*/serum	9
miR-1261	Upregulated	*In vivo*/serum	9
miR-1268	Upregulated	*In vivo*/serum	9

Abbreviations: miRNA, microRNA; NB, neuroblastoma.

REFERENCES

1 Zhu S, Lee J-S, Guo F, Shin J, Perez-Atayde AR, Kutok JL *et al.* Activated ALK collaborates with MYCN in neuroblastoma pathogenesis. *Cancer Cell* 2012; **21**: 362–373.
2 Brodeur GM. Neuroblastoma: biological insights into a clinical enigma. *Nat Rev Cancer* 2003; **3**: 203–216.
3 Gholamin S, Pasdar A, Sadegh Khorrami M, Mirzaei H, Reza Mirzaei H, Salehi R *et al.* The potential for circulating microRNAs in the diagnosis of myocardial infarction: a novel approach to disease diagnosis and treatment. *Curr Pharm Des* 2016; **22**: 397–403.
4 Mirzaei H, Gholamin S, Shahidsales S, Sahebkar A, Jafaari MR, Mirzaei HR *et al.* MicroRNAs as potential diagnostic and prognostic biomarkers in melanoma. *Eur J Cancer* 2016; **53**: 25–32.
5 Simonian M, Mosallayi M, Mirzaei H. Circulating miR-21 as novel biomarker in gastric cancer: diagnostic and prognostic biomarker. *J Cancer Res Ther* 2016. (e-pub ahead of print).
6 Reza Mirzaei H. Circulating microRNAs in hepatocellular carcinoma: potential diagnostic and prognostic biomarkers. *Curr Pharm Des* 2016. (e-pub ahead of print).
7 Salarini R, Sahebkar A, Mirzaei H, Jaafari M, Riahi M, Hadjati J *et al.* Epi-drugs and epi-miRs: moving beyond current cancer therapies. *Curr Cancer Drug Targets* 2015. (e-pub ahead of print; 6 December 2015).
8 Ghossein RA, Bhattacharya S, Rosai J. Molecular detection of micrometastases and circulating tumor cells in solid tumors. *Clin Cancer Res* 1999; **5**: 1950–1960.
9 Ramraj SK, Pandian V, Khan FH, Aravindan S, Herman TS, Natarajan M *et al.* Profiling of circulating miRNAs is a critical prognostic biomarker tool for high-risk neuroblastoma. *Cancer Res* 2014; **74**: 5229.
10 Combaret V, Bergeron C, Bréjon S, Iacono I, Perol D, Négrier S *et al.* Protein chip array profiling analysis of sera from neuroblastoma patients. *Cancer Lett* 2005; **228**: 91–96.