World Journal of Biomedical Sciences
ISSN: 2960-0189
DOI: 10.61784/wjbsv2n231

ABNORMAL EXPRESSION OF MICRORNA AND BIOMARKERS IN SOFT TISSUE SARCOMA

Toshiyuki Ochiya
Center for Innovative Clinical Medicine, Okayama University Hospital, Okayama 7008558, Japan.

Abstract: Soft tissue sarcoma is a highly heterogeneous malignant tumor derived from mesenchymal tissue. Due to its large number of histological subtypes and clinical and histopathological uncertainties, current diagnosis and treatment are very difficult. One of the important clinical issues is the lack of useful biomarkers; therefore, the discovery of biomarkers that can be used to detect tumor response to chemotherapy or radiotherapy may help clinicians provide more effective clinical management. Studying microRNA in soft tissue sarcomas provides clues to solving the problem. The discovery of evidence such as differential microRNA in soft tissue sarcoma and circulating microRNA in patient serum has the potential to accelerate the transition to clinical application, which undoubtedly brings new hope for the eradication of soft tissue sarcoma.
Keywords: MicroRNA; Soft tissue sarcoma; Biomarkers; Treatment

1 ABNORMAL MICRORNA IN SOFT TISSUE SARCOMA

When the miRNA gene was found to be deleted in leukemia, the importance of miR-NA in malignant diseases began to be recognized. Research reports show that miRNAs are misregulated in many malignant tumors, and these misregulated miRNAs can trigger carcinogenesis or promote its progression. Dysregulation of miRNAs can result from either genetic or epigenetic changes, and many miR-NAs are located within chromosomal fragile sites, and these are often deleted or rearranged in malignant tumors.

1.1 Leiomyosarcoma

LMS is a malignant sarcoma formed by abnormal differentiation and expression of smooth muscle cells. Surgical resection is the most reliable treatment. The effect of chemotherapy and radiotherapy is not very clear, but chemotherapy and radiotherapy can be used as an auxiliary treatment for postoperative patients to improve the patient's survival rate. In a comparative study of the miRNAs in LMS and leiomyomas, some benign lesions, and other soft tissue sarcomas, it was found that the miRNAs in LMS were up-or down-regulated. Subramanian reported that the miR-1, -133a, -133b of LMS were significantly up-regulated compared with normal smooth muscle, and miR-1, -133a, -133b played an important role in myogenesis and myoblast proliferation [1]. When Guled studied LMS and UPS chips, he found and determined that miR-320A was up-regulated in LMS relative to UPS [2]. Similarly, Reina et al. reported that miR-133a, -1, and -449a were up-regulated, while miR-483-5p, -656, and -323-3p were down-regulated in LMS compared with other sarcoma subtypes [3]. These results are partly consistent with Subramanian's views. Nuovo found that LMSmiR-221 was upregulated in the uterus during in situ hybridization, but it was not detected in leiomyomas or benign metastases of fibroids [4].

1.2 Pleomorphic Undifferentiated Sarcoma

Malignant fibrous histiocytoma (MFHs) was first described in 1963. "Malignant fibrous histiocytoma" means that the tumor cells originate from fibroblasts and histiocytes. In 2002, the WHO proposed MFH as a formal diagnostic entity and changed its name to pleomorphic undifferentiated sarcoma (UPS). In 2013, UPS/MFH was classified as undifferentiated/unclassified sarcoma [5]. Guled and colleagues used miRNA expression profiling to characterize a range of samples, looking for specific markers that could be used for differential diagnosis. Analyzing 10 LMS and 10 UPS, cultured human bone marrow mesenchymal stem cells were used as the control group. When comparing human miRNA with control samples, significant differences in miRNA expression were found [2]. When UPS samples were compared with the control group[2], miR-126, -223, -451, -1274b were significantly up-regulated, while miR-100, -886-3p, -1260, -1274a and 1274b were significantly down-regulated. In addition, some genes IMP3, Ror2, MDM2, CDK4 and uPA were found to be targets of differentially expressed miRNAs. Its expression has been demonstrated by immunohistochemistry.

1.3 Liposarcoma

Liposarcoma is divided into the following four major types: well-differentiated liposarcoma (WDLSs), myxoid liposarcoma (MLSs), pleomorphic liposarcoma (PLSs), and dedifferentiated liposarcoma (DDLSs). More than 40 miRNAs were found to be dysregulated in DDLS and WDLS, including up-regulation of miR-21 and -26 and down-regulation of miR-143, and -145. In DDLS cells, re-expression of miR-143 inhibits cell proliferation and induces apoptosis by down-regulating Bcl-2, topoisomerase IIα, cytokinesis regulatory protein 1, and Polo-like kinase 1 [6]. miR-155 has inhibitory effects on cell growth and colony formation in DDLS, and inhibits tumor growth by arresting the G1 cell cycle. In comparison with normal adipose tissue, Taylor confirmed that miR-193b is downregulated[7].

Hisaoka determined that mir-1257 is downregulated, mir-The target of 1257 is calretic histone, which has the effect of inhibiting adipocyte differentiation [8]. Recently, the clinical relevance of miRNA dysregulation in liposarcoma has been demonstrated. Lee studied a single sample of 75 liposarcoma patients using SNP array samples. It was determined that mir-26a-2c is frequently amplified and upregulated in WDLS/DDLS and MLS [9]. Furthermore, high mir-26a-2 expression was significantly associated with patient survival regardless of histological subtype. Chromosome condensation and BTB domain protein 1 are both considered to be one of the targets of mir-26a-2, regulating apoptosis [9].

1.4 Rhabdomyosarcoma (RMS)

RMS is the most common soft tissue sarcoma in children under 15 years of age. RMS pathology is divided into the following four subtypes: embryonal rhabdomyosarcoma (ERMS), alveolar RMS (aRMS), pleomorphic RMS (PRMS), and spindle cell/sclerosing RMS. Muscle-specific miRNAs involved in skeletal muscle development have become a focus of attention in many studies [10-11].

The clinical relevance of these muscle tissue-specific miRNAs was demonstrated by Missiaglia et al. , who analyzed the expression of miR-1, -206, and -133B 133a in 163 RMS patients. A clinical correlation was determined between overall survival and expression of miR-206, whereas no correlation was found for miR-1 or 133a/b. Especially in metastatic eRMS and aRMS cases without PAX3/7-FOXO1 fusion gene, low miR-206 expression is associated with overall survival [12]. In another important research report on aRMS, Reichek studied the amplification of gene 13q31 containing the miR-17-92 gene cluster. 13q31 amplification occurs in 23% of aRMS cases, particularly in PAX7-FKHR positive cases. Importantly, overexpression of the miR-17-92 gene cluster was found to be significantly associated with poor prognosis in patients with gene 13q31 amplification [13]. miRNA and drug-resistant RMS are mainly reflected in the expression level of miR-485-3p. Chen conducted experiments again in drug-sensitive and drug-resistant RMS cells and found that the mir -485-3p-top2α-NF -YB pathway represents a new drug-sensitive phenomenon [14].

1.5 Synovial Sarcoma

Synovial sarcomas account for 5% of soft tissue sarcomas, and they are characterized by local invasion and tendency to metastasize. The tumor has a specific chromosomal translocation t (X; 18) (p11; q11), resulting in the formation of an SS18 – SSX fusion gene [15-17]. In 2008, Subramanian and colleagues were the first to discover miRNA in synovial sarcoma. Using microarray, cloning, and Northern blot analyses, they demonstrated that miR-143 was downregulated in synovial sarcoma relative to other sarcomas, gastrointestinal stromal tumor (GIST), and LMS. In the computer simulation database, SSX1 is a predicted target of miR-143, so it can be speculated that reducing miR-143 can initiate the production of ss18-ssx1 oncogene protein. Sarver has been focusing on the molecular characterization of synovial sarcoma and found that miR-183 plays an important role in carcinogenesis through the miR-183-EGR1-PTEN signaling pathway. A recent investigation by Minami showed that overexpression of miR-17-5 can increase cell growth and promote cell colony size [18].

1.6 Nervous Sheath Tumors (MPNSTs)

MPNSTs are malignant nerve sheath tumors arising from peripheral nerves. Subramanian et al. found that downregulation of miR-34a expression and P53 gene inactivation occurred in most MPNSTs. Therefore, they believe that p53 gene inactivation and downregulation of miR-34a expression may significantly contribute to the development of MPNST [19]. Some studies have used similar methods and determined that overexpression of miR-21 in MPNSTs and silencing of miR-21 in MPNST cell lines can induce apoptosis of tumor cells [20]. Presneau compared the miRNA expression profiles of MPNST and NFS and found two upregulated (miR-210 and 339-5p) and 14 downregulated miRNAs (miR-29c, 2006, -195, -139-5p, 151-5p, 342-5p, 146a, -150, -223) [21]. Zhang focused on the expression of zeste homologous chromosome 2 PcG protein enhancer (EZH2) and found that the EZH2-miR-30d-KPNB1 signaling pathway may be key to MPNST survival and tumorigenicity [22].

1.7 Angiosarcoma

Angiosarcomas are malignant tumors that retain many morphological and functional properties of normal endothelial cells. Significant dysregulation of miRNAs was found in angiosarcoma compared with other sarcomas. Italiano et al. compared gene amplification and myc amplification of miRNA profiles in angiosarcoma using miRNA library sequencing, and the miR-17-92 cluster was determined to be preferentially expressed in myc amplification. Myc amplification in angiosarcomas is associated with low expression of thrombospondin (THBS1), the first inhibitor of angiogenesis. Myc amplification may be important for the angiosarcoma phenotype through expression of the miR-17-92 gene cluster. Up-regulation can lead to down-regulation of THBS1 expression [23].

1.8 Fibrosarcomas

To date, miRNA expression profiles have not been studied in fibrosarcoma tissue specimens and have been limited to the HT1080 fibrosarcoma cell line. Liu and Wilson studied the correlation between matrix metalloproteinases (MMPs) and HT1080 fibrosarcoma cell line miR-520c and miR-373, which have been reported to play an important role in cancer cell metastasis. Their data showed that mir-520c and-373 inhibits the translation of mTOR and SIRT1 by acting directly on the 3′ untranslated region (UTR). Since mTOR and SIRT1 are negative regulators of MMP9 and can inactivate the Ras/Raf/MEK/ERK signaling pathway, these miRNAs increase the expression of MMP-9, directly target mTOR and SIRT1,

and stimulate cell growth and migration [24]. Weng et al. studied the HT1080 fibrosarcoma cell line and found that angiotensin mRNA was silenced or expressed by mir-409-3p through its 3′UTR and mir-409-3p in HT1080 cells. In vitro analysis showed that downregulation of mir-409-3p inhibited tumor growth, angiogenesis, metastasis and expression [25].

1.9 Epithelioid Sarcoma (ES)

Epithelioid sarcoma accounts for about 1% of all sarcomas. Clinicopathological classification: proximal type and distal type. The prognosis of patients with proximal type is worse than that of patients with distal type. Proximal epithelioid sarcomas share genetic similarities with MRTs, including nuclear deficiency in SMARCB1 (also known as INI1, BAF47, or hSNF5). Papp et al. found that miRNAs regulate SMARCB1 expression and analyzed 8 candidate miRNAs through bioinformatics. Quantitative PCR assay in epithelioid sarcoma and MRT samples found overexpression of miR-206, -381, -765, -671-5p in epithelioid sarcoma, among which, 3 upregulated miRNAs (miR-206, mir-381, and mir-671-5p) can silence the expression of SMARCB1mRNA, and the most effective microRNA is miR-206. Therefore, the loss of SMARCB1 expression in epithelioid sarcoma may be due to changes in epigenetic mechanisms caused by the expression of related miRNAs [26].

2 MIRNA AND BIOMARKERS

Abnormal expression of miRNA can cause abnormalities in cell differentiation, proliferation, and apoptosis, which are closely related to the occurrence and development of tumors. As a new molecular biological marker, it has important potential value in the diagnosis and treatment of tumors. Recent studies have shown that tumor cells can secrete miRNA into the blood circulation [27-29]. Analysis of miRNA levels in serum or plasma has become a new method for diagnostic cancer screening or monitoring. The expression of other circulating miRNAs in blood has been widely reported. So far, circulating miRNA has been reported in soft tissue sarcoma RMS and MPNST [30]. The study of circulating miRNA in body fluids has become one of the hot spots in many disciplines such as modern medicine, immunology, embryology, developmental biology, and microbiology.

2.1 Serum miRNA in RMS

In 2010, Miyachi conducted the first clinical experiment on circulating miRNAs as new biomarkers in soft tissue sarcomas using serum from RMS patients as specimens [31]. Muscle tissue-specific miRNAs (miR-1, -133a, -133B, and 206) were significantly upregulated in RMS tumor specimens, and the levels of these miRNAs were significantly higher than in normal patients. Among these muscle tissue-specific miRNAs, serum miR-206 has the highest sensitivity and specificity [31]. The results obtained in RMS patient serum are consistent with previous studies of RMS tissue, suggesting that differential expression of miRNAs can be reflected in patient serum.

2.2 Serum miRNA of MPNST

Weng et al have discovered the possibility of using miRNAs as non-invasive biomarkers for the diagnosis of MPNST. Genomic serum miRNA expression analysis was used to differentiate patients with MPNST from those with neurofibromatosis type I (NF1). People with NF1 have a higher risk of developing MPNST during their lifetime. Solexa sequencing was used to screen differentially expressed miRNAs in serum, and the results showed that MPNST patients had significantly higher expression of miR-214 and -801 than NF1 patients [31]. Furthermore, significant upregulation of miR-24 occurred in MPNST patients with NF1. Therefore, the combination of these three miRNAs (miR-24, -214, -801) can be used to distinguish MPNST from NF1 MPNST [32].

3 CONCLUSION

To date, few biomarkers have been used to diagnose and monitor soft tissue sarcomas. Over the past 30 years, genetic studies, such as the identification of fusion genes, have greatly improved the diagnosis of soft tissue sarcomas. However, these results only apply to limited histological subtypes; therefore, the identification of specific histological subtypes of miRNAs is a new breakthrough for sarcoma research. Identification of circulating miRNAs can serve as biomarkers reflecting drug resistance, which will help doctors determine the best individual treatment options, thereby improving patient prognosis and survival rates.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

REFERENCES

[1] Subramanian S, Lui WO, Lee CH. Micro RNA expression signature of human sarcomas. Oncogene, 2008, 27(14): 2015-2026.
[2] Guled M, Pazzaglia L, Borze I. Differentiating soft tissue leiomyosarcoma and undifferentiated pleomorphic sarcoma: a miRNA analysis. Genes Chromosomes Cancer, 2014, 53(8): 693-702.
[3] Renner M, Czwan E, Hartmann W. MicroRNA profiling of primary high-grade soft tissue sarcomas. Genes Chromosomes Cancer, 2012, 51(11): 982-996.

[4] Garofalo M, Jeon YJ, Nuovo GJ. Correction: MiR-34a/c-Dependent PDGFR-ery downregulation inhibits tumorigenesis and enhances TRAIL-induced apoptosis in lung cancer. Plos One, 2015, 10(6): 113-124.
[5] Fletcher CDM. The evolving classification of soft tissue tumours -an update based on the nwe 2013 WHO classification. Pathology, 2006, 64(1): 2-11.
[6] Ugras S, Brill E, Jacobsen A. Small RNA sequencing and functional characterization reveals MicroRNA-143 tumor suppressor activity in liposarcoma. Cancer Res, 2011, 71(17): 5659-5669.
[7] Taylor BS, Decarolis PL, Angeles CV. Frequent alterations and epigenetic silencing of differentiation pathway genes in structurally rearranged liposarcomas. Cancer Discov, 2011, 1(7): 587-597.
[8] Hisaoka M, Matsuyama A, Nakamoto M. Aberrant calreticulin expressionis involved in the dedifferentiation of dedifferentiated liposarcoma. Am J Pathol, 2012, 180(5): 2076-2083.
[9] Lee DH, Amanat S, Goff C. Abstract 4203: overexpression of miR-26a-2 in human liposarcoma is correlated with poor patient survival. Oncogenesis, 2013, 2(5): 47.
[10] Giešla M, Dulak J, Józkowicz A. MicroRNAs and epigenetic mechanisms of rhabdomyosarcoma, development. Int J Biochem Cell Biol, 2014, 53(8): 482-492.
[11] NovákJ, VinklárekJ, Ondex J. MicroRNAs involved in skeletal muscle development and their roles in rhabdomyosarcoma pathogenesis. Pediatr Blood Cancer, 2013, 60(11): 1739-1746.
[12] Missiaglia E, Shepherd CJ, Patel S. MicroRNA-206 expres sion levels correlate with clinical behaviour of rhabdomyosarcomas. Br J Cancer, 2010, 102(12): 1769-1777.
[13] Rota R, Ciarapica R, Giordano A. MicroRNAs in rhabdomyo-sarcoma: pathogenetic implications and translational potentiality. Molecular Cancer, 2011, 10(27): 2140-2145.
[14] Chen CF, He XL, Arslan AD. Novel regulation of nuclear factor-YB by miR-485-3p affects the expression of DNA topoisomerase IIα and drug responsiveness. Molecular Pharmacol, 2011, 79(4): 735-741.
[15] Wakamatsu T, Naka N, Sasagawa S. Deflection of vascular endothelial growth factor action by SS18-SSX and composite vascularendothelial growth factor-and chemokine (C-X-C motif) receptor 4-targeted therapy in synovial sarcoma. Cancer Sci, 2014, 105(9): 1124-1134.
[16] Kubo T, Shimose S, Fujimori J. Prognostic value of SS18-ssx of SS184-targeted therapy in synovial sarcoma: systematic review and meta-analysis. Springerplus, 2015, 4(1): 1-7.
[17] Tamaki S, Fukuta M, Sekiguchi K. SS18-SSX, the oncogenic fusion protein in synovial sarcoma, is a cellular context-dependent epigenetic modifier. Plos One, 2015, 10(11): e0142991.
[18] Minami Y, Kohsaka S, Tsuda M. SS18-SSX-regulated miR-17 promotes tumor growth of synovial sarcoma by inhibiting p21WAF1/CIP1. Cancer Sci, 2014, 105(9): 1152-1159.
[19] Subramanian S, Thayanithy V, West RB. Genome-wide transcriptome analyses reveal p53 inactivation mediated loss of miR-34a expression in malignant peripheral nerve sheath tumours. Experientia, 2010, 220(1): 58-70.
[20] Itani S, Kunisada T, Morimoto Y. MicroRNA-21 correlates with tumorigenesis in malignant peripheral nerve sheath tumor (MPNST)via programmed cell death protein 4(PDCD4). J Cancer Res Clin Oncol, 2012, 138(9): 1501-1509.
[21] Presneau N, Eskandarpour M, Shemais T. MicroRNA profiling of peripheral nerve sheath tumours identifies miR-29c as atumour suppressor gene involved in tumour progression. Br J Cancer, 2013, 108(4): 964-972.
[22] Zhang P, Garnett J, Creighton CJ. EZH2-miR-30d-KPNB1 pathway regulates malignant peripheral nerve sheath tumour cell survival and tumourigenesis. J Pathol, 2014, 232(3): 308-318.
[23] Italiano A, Thomas R, Breen M. The miR cluster and its target THBS1 are differentially expressed in angiosarcomas dependent on MYC amplification. Genes Chromosomes Cancer, 2012, 51(6): 569-578.
[24] Liu P, Wilson MJ. miR-520c and miR-373 upregulate MMP9 expression by targeting mTOR and SIRT1, and activate the Ras/Raf/ MEK/Erk signaling pathway and NF-kB factor. J Cellular Physiol, 2012, 227(2): 867-876.
[25] Weng C, Dong H, Chen G. miR-409-3p inhibits HT1080 cell proliferation , vascularization and metastasis by targeting angiogenin. Cancer Lett, 2012, 323(2): 171-179.
[26] Papp G, Krausz T, Stricker TP. SMARCB1, expression in epithelioid sarcoma is regulated by miR-206, miR-381, and miR-671-5p on both mRNA and protein levels. Genes Chromosomes Cancer, 2014, 53(2): 168-176.
[27] Cantara S, Pilli T, Sebastiani G. Circulating miRNA95 and miRNA190 are sensitive markers for the differential diagnosis of thyroid nodules in a Caucasian population. J Clin Endocrinol Metabolism, 2014, 99(11): 4190-4198.
[28] Duroux-Richard I, Pers YM, Fabre S. Circulating miRNA-125b is a potential biomarker predicting response to rituximab in rheumatoid arthritis. Mediators Inflammation, 2014, 2014(23): 342524.
[29] El-Abd NE, Fawzy NA, El-Sheikh SM. Circulating miRNA- 122, miRNA-199a, and miRNA-16 as biomarkers for early detec tion of hepatocellular carcinoma in egyptian patients with chronic hepatitis C virus infection. Molecular Diagnosis Ther, 2015, 19 (4): 213-220.
[30] Fujiwara T. Circulating MicroRNAs in sarcoma: potential biomarkers for diagnosis and targets for therapy. 2014, 3(123): 2.
[31] Miyachi M, Tsuchiya KH, Yagyu S. Circulating muscle-specific microRNA, miR-206, as a potential diagnostic marker for rhabdomyosarcoma. Biochem Biophysical Res Comm, 2010, 400 (1): 89-93.
[32] Weng Y, Chen Y, Chen J. Identification of serum microRNAs in genome-wide serum microRNA expression profiles as novel noninvasive biomarkers for malignant peripheral nerve sheath tumor diagnosis. Med Oncol, 2013, 30(2):1-6.