

Mini Review

The Role of MicroRNA in Ewing's Sarcoma

Sohn EJ*

College of Korean Medicine, University of Kyung Hee, South Korea

*Corresponding author: Sohn EJ, College of Korean Medicine, University of Kyung Hee, Dongdaemun-gu, South Korea

Received: October 19, 2016; Accepted: December 01, 2016; Published: December 03, 2016

Abstract

The Ewing's sarcoma is very aggressive and bone tumor arising in children and adolescent. Ewing Sarcoma (EWS) tumors resulted from chromosomal translocation between the EWSR1 gene and ETS members. MicroRNAs (miRNAs), as non-coding RNAs play an important role in cancer acting as both suppressors and oncogenes. Also, microRNAs involve in malignant phenotype or metastasis of Ewing sarcoma tumor. Understanding biological aspects of miRNA may give important information for pathogenesis of Ewing's sarcoma.

Keywords: Ewing's sarcoma; MicroRNA; ETS

Introduction

The Ewing's Sarcoma (EWS) is very aggressive and second malignant bone tumor after osteosarcoma arising in young [1]. EWS tumors resulted from chromosomal translocation between the EWSR1 gene located on chromosome 22 and Ewing's Family Tumors (ETS) members such as leukemia virus integration 1 (FLI), Fifth Ewing Sarcoma Variant (FEV), ETS-Related Gene(ERG), or ETS Variant Gene1(ETV1) [2-4]. Chromosomal translocations of fusion are as follows; EWS/FLI-1 t(11;22)(q24;q12), EWS/FEV1 t(2;22)(q35;q12), EWS/ERG t(21;22)(q22;q12), EWS/ETV1 t(7;22)(p22;q12) [5]. In 85% of Ewing's sarcoma, the ETS domain is resulted from 11q24 (FLI-1), producing an EWS/FLI-1 chimera by a t(11;22)(q24;q12) translocation [6]. Though radiotherapy, surgical resection, and multiagent chemotherapy have improved the survival outcome in Ewing sarcoma patients [7-9], the survival after relapse or with metastasis in the Ewing sarcoma patient is still low [10].

MicroRNAs

MicroRNAs (miRNAs) are non-coding RNAs involving in post transcriptional regulation [11]. Also, microRNA binds to the complementary sequences in the 3'UTR (the three prime Untranslated Region) to degrade or inhibit of target mRNAs. MiRNAs was involved in various cellular processes such as aging [12], apoptosis [13], and metastasis [14]. MicroRNA acts both as suppressors or oncogenes in cancer [15]. Also, MicroRNA acts as a prognostic indicator because of its stability and robust expression within clinical samples [16].

The Biological Roles of MicroRNA in Ewing's Sarcoma

Several studies showed that MicroRNA expression was altered in EWS tumor. Thirty five different microRNAs in Ewing sarcoma were identified from the Ewing sarcoma tumor and cell lines [17]. Among these, miRNA-106b, miRNA-93, miRNA-181b, miRNA-101, and miRNA-30b were highly expressed, while the expression of miRNA-145, miRNA-193a-3p, miRNA-100, miRNA-22, miRNA-21, and miRNA-574-3p was low from the Xenograft Ewing sarcoma model [18]. Eun et al reported that the expression of mature let 7g was low in Ewing sarcoma compared to osteosarcoma [19] miRNA 34a was expressed at the low level in Ewing sarcoma tumor [20]. The profile of MicroRNA expression could be important in diagnosis and understanding clinical source of EWS.

Michal et al reported that that let-7 negatively regulates HIF, which is an aggressive metastatic factor in Ewing's Sarcoma [21]. Li et al. also reported that miRNA-31 showed the proliferative and invasive abilities in Ewing sarcoma cell line suggesting as a tumor suppressor in Ewing's sarcoma [22]. Zhang et al showed that let-7a repressed malignant phenotype of Ewing's sarcoma via targeting STAT 3, and NF-kappa B [23]. Thus, these studies imply that MicroRNA may be essential in the tumorigenesis of Ewing's sarcoma.

Conclusion

Recently, MicroRNA has been suggested as a promising therapeutic target for cancer treatment. Finding a novel intracellular signaling pathway targeting of microRNAs in Ewing sarcoma pathogenesis may provide important source in diagnosis. Therefore, understanding the role of MicroRNA in Ewing's sarcoma is providing important information for therapeutic targets in Ewing's sarcoma.

Acknowledgement

This work was supported by the National Research Foundation of Korea (NRF) grant funded by Basic Research Program (2015R1C1A1A02036842).

References

1. Brasme JF, Morfouace M, Grill J, Martinot A, Amalberti R, Catherine Bons-Letouzey, et al. Delays in diagnosis of paediatric cancers: a systematic review and comparison with expert testimony in lawsuits. *Lancet Oncol.* 2012; 13: 445-459.
2. Tomlins SA, Mehra R, Rhodes DR, Smith LR, Roulston D, Helgeson BE, et al. TMPRSS2:ETV4 gene fusions define a third molecular subtype of prostate cancer. *Cancer Res.* 2006; 66: 3396-3400.
3. Tomlins SA, Laxman B, Dhanasekaran SM, Helgeson BE, Cao X, Morris DS, et al. Distinct classes of chromosomal rearrangements create oncogenic ETS gene fusions in prostate cancer. *Nature.* 2007; 448: 595-599.
4. Helgeson BE, Tomlins SA, Shah N, Laxman B, Cao Q, Prensner JR, et al. Characterization of TMPRSS2:ETV5 and SLC45A3:ETV5 gene fusions in prostate cancer. *Cancer Res.* 2008; 68: 73-80.
5. Sankar S, Lessnick SL. Promiscuous partnerships in Ewing's sarcoma. *Cancer Genet.* 2011; 204: 351-65.
6. Turc-Carel C, Aurias A, Mugneret F, Lizard S, Sidaner I, Volk C, et al. Chromosomes in Ewing's sarcoma. I. An evaluation of 85 cases of remarkable consistency of t(11;22)(q24;q12). *Cancer Genet Cytogenet.* 1988; 32: 229-238.
7. Subbiah V, Anderson P, Lazar AJ, Burdett E, Raymond K, Ludwig JA.

- Ewing's sarcoma: standard and experimental treatment options. *Curr Treat Options Oncol*. 2009; 10: 126-140.
8. Burdach S, Jurgens H. High-dose chemoradiotherapy (HDC) in the Ewing family of tumors (EFT). *Crit Rev Oncol Hematol*. 2002; 41: 169-89.
 9. Bacci G, Picci P, Ferrari S, Mercuri M, Brach del Prever A, Rosito P, et al. Neoadjuvant chemotherapy for Ewing's sarcoma of bone: no benefit observed after adding ifosfamide and etoposide to vincristine, actinomycin, cyclophosphamide, and doxorubicin in the maintenance phase--results of two sequential studies. *Cancer*. 1998; 82: 1174-1183.
 10. Stahl M, Ranft A, Paulussen M, Bölling T, Vieth V, Bielack S, et al. Risk of recurrence and survival after relapse in patients with Ewing sarcoma. *Pediatr Blood Cancer*. 2011; 57: 549-553.
 11. Obernosterer G, Leuschner PJ, Alenius M, Martinez J. Post-transcriptional regulation of microRNA expression. *RNA*. 2006; 12: 1161-1167.
 12. Singh J, Boopathi E, Addya S, Phillips B, Rigoutsos I, Penn RB, et al. Aging-associated changes in microRNA expression profile of internal anal sphincter smooth muscle: role of microRNA-133a. *Am J Physiol Gastrointest Liver Physiol*. 2016.
 13. Jafarnejad-Farsangi S, Farazmand A, Gharibdoost F, Karimizadeh E, Noorbakhsh F, Faridani H, et al. Inhibition of MicroRNA-21 induces apoptosis in dermal fibroblasts of patients with systemic sclerosis. *Int J Dermatol*. 2016; 55: 1259-1267.
 14. Ma L. MicroRNA and Metastasis. *Adv Cancer Res*. 2016; 132: 165-207.
 15. Joung JG, Kyu-Baek Hwang, Jin-Wu Nam, Soo-Jin Kim, Byoung-Tak Zhang. Discovery of microRNA-mRNA modules via population-based probabilistic learning. *Bioinformatics*. 2007; 23: 1141-1147.
 16. Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, et al. MicroRNA expression profiles classify human cancers. *Nature*. 2005; 435: 834-838.
 17. Karnuth B, Nicolas Dedy, Tilmann Spieker, Lawlor ER, Stefan Gattenlöhner, Andreas Ranft, et al. Differentially expressed miRNAs in Ewing sarcoma compared to mesenchymal stem cells: low miR-31 expression with effects on proliferation and invasion. *PLoS One*. 2014; 9: 93067.
 18. Mosakhani N, Mohamed Guled, Gayle Leen, Silvia Calabuig-Fariñas, Tarja Niini, Isidro Machado, et al. An integrated analysis of miRNA and gene copy numbers in xenografts of Ewing's sarcoma. *J Exp Clin Cancer Res*. 2012; 31: 24.
 19. Sohn EJ, Park J, Kang SI, Wu YP. Accumulation of pre-let-7g and downregulation of mature let-7g with the depletion of EWS. *Biochem Biophys Res Commun*. 2012; 426: 89-93.
 20. Marino MT, Grilli A, Baricordi C, Manara MC, Ventura S, Pinca RS, et al. Prognostic significance of miR-34a in Ewing sarcoma is associated with cyclin D1 and ki-67 expression. *Ann Oncol*. 2014; 25: 2080-2086.
 21. Hameiri-Grossman M, Porat-Klein A, Yaniv I, Ash S, Cohen IJ, Kodman Y, et al. The association between let-7, RAS and HIF-1alpha in Ewing Sarcoma tumor growth. *Oncotarget*. 2015; 6: 33834-33848.
 22. Li Z, Yu X, Shen J, Wu WK, Chan MT. MicroRNA expression and its clinical implications in Ewing's sarcoma. *Cell Prolif*. 2015; 48: 1-6.
 23. Zhang Z, Li Y, Huang L, Xiao Q, Chen X, Zhong J, et al. Let-7a suppresses macrophage infiltrations and malignant phenotype of Ewing sarcoma via STAT3/NF-kappaB positive regulatory circuit. *Cancer Lett*. 2016; 374: 192-201.