Can MicroRNAs be Revolutionary Biomarkers in Oligometastatic Paradigm?

Abstract

MicroRNAs are considered a discovery that helps us to comprehend tumorigenesis. The use of MicroRNAs in clinical trials is still humble. However, there are significant steps forward for the use of MicroRNAs at daily practice; when dealing with an oligometastatic situation. This review will present the emerging role of microRNAs in oligometastatic setting and also their possible role in local therapy paradigm.

Keywords: MicroRNA; miRNA; Oligometastases; Metastases; Radiation; Surgery; Stereotactic body radiotherapy; Stereotactic ablative radiotherapy

Introduction

Oligometastases are metastases that are limited in number and location. Hellman and Weichselbaum coined this term in 1995 [1]. They hypothesized that patients with less aggressive tumors and few new metastases during the first four months of first metastatic progression could potentially benefit from metastasis-directed therapy. They also identified a class of small RNAs, known as microRNAs, which might help distinguish patients with stable oligometastatic disease from patients with progression to poly metastatic disease. Oligometastases produced by the early progression of primary lesions are known as de novo. “oligometastases” whereas widespread metastases correspond to a state of “induced oligometastases” [2,3].

Tumorigenesis is a complicated process that contains short and long distance communications between tumor cells and hostile environment to survive, progress and metastasize. The short distance communications include interactions between tumor cells themselves and tumor cells with the host cells through manipulation of the microenvironment, hence optimizing tumor growth, invasion, and survival [4,5]. On the other hand, long distance communications with stromal cells lead to pre-metastatic niche formation, encouraging colonization and metastases [6]. These communications involve the transport of various proteins, lipids and nucleic acids via membranous compartments done by tumor-derived exosomes, which also transfer MicroRNA [7,8]. MicroRNAs are considered a discovery that helped us to comprehend the tumorigenesis. These are short noncoding RNAs which target and block complementary messenger RNAs, as well as play a master role in regulating genes’ expression and protein synthesis [9,10]. An individual target gene can be regulated by several microRNAs, moreover a single MicroRNA can lead countless genes. Therefore, specific MicroRNAs might influence and regulate the oligometastatic phenotype [11].

This review will present the emerging role of microRNAs in oligometastatic setting and also their possible role in local therapy paradigm.

Discussion

The clinical studies that correlate microRNAs with clinical outcomes are still scarce. Regarding the same there are only a few studies on limited metastases and a small / large cohort of tumor samples. In these studies local treatment was either hypofractionated radiation [12], stereotactic body radiation [13], or surgery [14].

In one of the studies that had the smallest size of samples, 17 Samples of primary tumor tissue with 12 different histologies, showed a lack of overlap between the microRNA subtypes. Heterogeneity of samples and prognostic correlation with survival rather than metastatic progression can be the cause of that absence [13]. Moreover, since the number of samples is less a significant conclusion could not have been drawn. In that study, MicroRNA-23b was non-significantly over expressed in patients who had oligometastases with more than 3-year survival. On the contrary, MicroRNA-449a and MicroRNA-449b were non-significantly over expressed in those with less than 3-year survival [13].

In a second study, a heterogeneous group of 42 primary and metastatic tumor samples were selected. MicroRNA-200b and MicroRNA-200c are highly expressed in the metastatic tissues from oligometastatic patients, who later progress to polymetastases. To enhance the micrRNA-200 family validation,
three kinds of animal models were used; for the discrimination of oligo- and polymetastases, stable conversion oligometastasis(es) to polymetastatic progression (via MicroRNA-200c), and thirdly augmenting the lung colonization efficiency. Internal consistency between various different analysis methods reinforces the validity of the clinical findings. MicroRNAs selected from primary samples revealed good discrimination between oligometastases and widespread polymetastases; in the metastatic sample set. Conversely the application of selected metastatic microRNA to primary samples was less. This evidence can partially clarify the question regarding the utility of MicroRNA and selection of samples for the predictive value [12].

The same author and his associates studied a larger, more homogeneous group of patients with resected lung metastasis. In this study, new groups of patients were identified which included patients with a low rate of recurrence (LRP), patients with a high rate of recurrence (HRP), and patients with an intermediate rate of recurrence (IRP). Oligometastases (OM) and polymetastases (PM) that entitled at the previous study were represented by LRP and HRP, respectively. Comparison of deregulated microRNAs expression between the two classifications (new vs. old one) was made to find the overlap between them. MicroRNA-328 and MicroRNA-502-5p overlapped in both classifications and were down-regulated in HRP and PM patient samples. Also, three members of the microRNA-154 family were under-expressed in HRP samples as compared to LRP samples in the lung metastasis dataset [14].

The down-regulation of Micro-RNAs at the late phase of metastases meant higher activity of tumorigenesis [15] and considered as a bad sign for local treatment efficacy. The main findings of the largest study were identification of microRNA-154 family which is down-regulated at the late phase of metastases [14]. MicroRNA-154 can suppress tumor cell growth in the G1/S phase [16]. Lower-rate of overlap of microRNA expression between two large studies may be related to differences in the patient cohorts [17] and heterogeneity of histopathology reported in the first article. MicroRNA-23b expression linked with improved PFS or OS in patients with ovarian, prostate, and renal cancer [18-20] but with worse results in breast cancer patients [21]. MicroRNA-449b expression augments the recurrence risk in prostate cancer patients [22]. MicroRNA-449a and MicroRNA-449b also have tumor-suppressive effects in vitro setting [23-25]. Similarly, microRNA-200 family can prevent a primary tumor from progressing to metastasis by maintaining an epithelial phenotype [26]. Other studies revealed the correlation between microRNA-200 family and efficient metastatic colonization [27,28]. The conflicting effects of microRNA mirrored the complexity of the relation between tumorigenesis and microRNAs [13].

Conclusion

MicroRNAs are feasible tool to predict oligometastatic progression. MicroRNAs might be added to Patient/tumor factors to define the indication of local treatment at an oligometastatic level, in near future. Larger cohorts of patients/ higher homogeneity of samples are necessary to augment the accuracy of the microRNA.

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References

1. Hellman S, Weichselbaum RR (1995) Oligometastases. Journal of Clinical Oncology 13(1): 8-10.
2. MacDermid DM, Weichselbaum RR, Salama JK (2008) A rationale for the targeted treatment of oligometastases with radiotherapy. J Surg Oncol 98(3): 202-206.
3. Almaghrabi MY, Supiot S, Paris E, Mahe MA, Rie O (2012) Stereotactic body radiation therapy for abdominal oligometastases: A biological and clinical review. Radiat Oncol 7: 126.
4. Bruecher BL, Jamali IS (2014) Cell-cell communication in the tumor microenvironment, carcinogenesis, and anticancer treatment. Cell Physiol Biochem 34(2): 213-243.
5. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144(5): 646-674.
6. Sceney J, Smyth MJ, Möller A (2013) The pre-metastatic niche: finding common ground. Cancer Metastasis Rev 32(3-4): 449-464.
7. Tickner JA, Uruquhart AJ, Stephenson SA, Richard DJ, O’Byrne KJ (2014) Functions and therapeutic roles of exosomes in cancer. Front Oncol 4: 127.
8. Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, et al. (2007) Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol 9(6): 654-659.
9. Bartel DP (2004) MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 116(2): 281-297.
10. Xu K, Lin J, Zandi R, Roth JA, Ji L (2016) MicroRNA-mediated target mRNA cleavage and 3′-uridylation in human cells. Sci Rep 6: 30242.
11. Uppal A, Wightman SC, Mallon S, Oshima G, Pitroda SP, et al. (2015) 14q32-encoded microRNAs mediate an oligometastatic phenotype. Oncotarget 6(6): 3540-3552.
12. Lussier YA, Xing HR, Salama JK, Khodarev NN, Huang Y, et al. (2011) MicroRNA expression characterizes oligometastasis(es). PLoS One 6(12): e28650.
13. Wong AC, Watson SP, Pitroda SP, Son CH, Das LC, et al. (2016) Clinical and molecular markers of long-term survival after oligometastasis-directed stereotactic body radiotherapy (SBRT). Cancer 122(14): 2242-2250.
14. Lussier YA, Khodarev NN, Regan K, Corbin K, Li H, et al. (2012) Oligo- and polymetastatic progression in lung metastasis(es) patients is associated with specific microRNAs. PLoS One 7(12): e50141.
15. Kimar MS, Lu J, Mercer KL, Gohib TR, Jacks T (2007) Impaired microRNA processing enhances cellular transformation and tumorigenesis. Nat Genet 39(5): 673-677.
16. Wang W, Peng B, Wang D, Ma X, Jiang D, et al. (2011) Human tumor microRNA signatures derived from large-scale oligonucleotide microarray datasets. Int J Cancer 129(7): 1624-1634.
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17. Fan C, Oh DS, Wessels L, Weigelt B, Nuyten DS, et al. (2006) Concordance among gene-expression-based predictors for breast cancer. N Engl J Med 355(6): 560-569.

18. Li W, Liu Z, Chen L, Zhou L, Yao Y (2014) MicroRNA-23b is an independent prognostic marker and suppresses ovarian cancer progression by targeting runt-related transcription factor-2. FEBS Lett 588(9): 1608-1615.

19. Majid S, Dar AA, Saini S, Arora S, Shahryari V, et al. (2012) miR-23b represses proto-oncogene Src kinase and functions as methylation-silenced tumor suppressor with diagnostic and prognostic significance in prostate cancer. Cancer Res 72(24): 6435-6446.

20. Zaman MS, Thamminana S, Shahryari V, Chiyomaru T, Deng G, et al. (2012) Inhibition of PTEN gene expression by oncogenic miR-23b-3p in renal cancer. PLoS One 7(11): e50203.

21. Jin L, Wessely O, Marcusson EG, Ivan C, Calin GA, et al. (2013) Prooncogenic factors miR-23b and miR-27b are regulated by Her2/Neu, EGF, and TNF-alpha in breast cancer. Cancer Res 73(9): 2884-2896.

22. Mortensen MM, Hoyer S, Orntoft TF, Sorensen KD, Dyrskjot L, et al. (2014) High miR-449b expression in prostate cancer is associated with biochemical recurrence after radical prostatectomy. BMC Cancer 14: 859.

23. Kheir BT, Kazmierczak FE, Jacobsen A, Krogh A, Bardram L, et al. (2011) miR-449 inhibits cell proliferation and is down-regulated in gastric cancer. Mol Cancer 10: 29.

24. Chen SP, Liu BX, Xu J, Pei XF, Liao YJ, et al. (2015) miR-449a suppresses the epithelial mesenchymal transition and metastasis of hepatocellular carcinoma by multiple targets. BMC Cancer 15: 706.

25. Yang X, Feng M, Jiang X, Wu Z, Li Z, et al. (2009) miR-449a and miR-449b are direct transcriptional targets of E2F1 and negatively regulate pRb-E2F1 activity through a feedback loop by targeting CDK6 and CDC25A. Genes Dev 23(20): 2388-2393.

26. Gregory PA, Bert AG, Paterson EL, Barry SC, Tsykin A, et al. (2008) The miR200 family and miR-205 regulate epithelial-to-mesenchymal transition by targeting ZEB1 and SIP1. Nat Cell Biol 10(5): 593-601.

27. Korpal M, Ell BJ, Buffa FM, Ibrahim T, Blanco MA, et al. (2011) Direct targeting of Sec23a by miR-200s influences cancer cell secretome and promotes metastatic colonization. Nat Med 17(9): 1101-1108.

28. Schwab EI, Lorentzen A, Marshall CJ (2010) MicroRNA-200 family members differentially regulate morphological plasticity and mode of melanoma cell invasion. PLoS One 5(10): e13176.