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Can MicroRNAs be Revolutionary Biomarkers in Oligometastatic Paradigm?

Abstract

Micro RNAs 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

Review Article

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Abbreviations: LRP: Low Rate of Recurrence; HRP: High Rate of Recurrence; IRP: Intermediate Rate of Recurrence; OM: Oligometastases; PM: Polymetastases

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 oligometastates 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 tumorogenesis [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 G (1)/S [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, micrRNA-200 family can prevent a primary tumor from progressing to metastasis by maintaining an epithelial phenotype [26]. Other studies revealed the correlation between micrRNA-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 oligometastaic 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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