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Usage of MicroRNA in Potential Therapeutics of Ewing's Sarcoma

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Abstract

MicroRNAs (miRs) have recently emerged as important regulators of intracellular gene expression. In miR, which is often dysregulated in cancer, sheds new light on the molecular mechanisms of carcinogenesis and is of great interest as a biomarker and new therapies and targets. Recently, many studies have investigated the miR biology of Ewing sarcoma. The results indicate that changes in miR expression are widespread in Ewing sarcoma, including both carcinogenic EWS / Ets fusion-dependent and independent mechanisms, and contribute to a malignant phenotype. MiRs with potential prognosis have been identified, and several preclinical studies suggest that miR manipulation may be therapeutically useful for this invasive disease.

Keywords: RNA; Sarcoma; Malignant; Carcinogenic

Introduction

MicroRNAs (miRs) represent a recently discovered new class of cell bioactive molecules that have important functions in the regulation of gene expression in normal physiology and disease [1]. MiRs are short (20-30 nt) single-stranded RNA molecules that bind to mRNA (mRNA) molecules that encode proteins primarily in the 3'untranslated region (UTR). This binding reduces the synthesis of the encoded protein through a variety of mechanisms, including increased mRNA degradation and inhibition of translation. Bindings are sequence-specific, but contain limited (~ 6–8) nt matches [2]. Therefore, individual miRs have many potential mRNA targets, and miRs as a group help control many expressions in the genome.

MicroRNAs are derived from hairpin-type double-stranded precursors (pre-miRs) by the action of protein complexes containing the Dicer gene product [3, 4, 5].

Most of these progenitors are derived from longer primary transcripts (pri-miR) by the action of microprocessor complexes containing the proteins Drosha and DGCR8 [3-5]. Some miRs are embedded in the gene encoding the protein and co-regulated with the parent mRNA, but about half are derived from independent non-protein coding transcripts under the control of the RNA polymerase II-driven promoter. The expression of such miRs is affected by the same promoter regulatory mechanisms as the genes encoding proteins, including the action of specific transcription factors. Currently, relatively little is known about the exact mechanism that regulates miR expression under normal homeostatic conditions and diseases.

In cancer, miR functions as a tumor suppressor or tumor gene depending on the situation, and through its molecular function as a regulator of gene expression, tumor cell proliferation / apoptosis, infiltration / metastasis, strain-like characteristics, angiogenesis, etc., Can change any aspect of tumorigenesis [6, 7]. Importantly, miR represents a promising new treatment or / and target, a concept validated in preclinical studies. Such studies show that administration of a chemical mimic of tumor suppressor miR or a chemical antagonist of tumorigenic miR can have a strong impact on tumor growth and / or spread in animal models of the disease rice field. Examples of successful preclinical treatment trials in childhood cancer include miR-380-5p replacement [8, 9, 10] in neuroblastoma, and miR replacement with miR-100 and miR-371 clusters in hepatoblastoma / includes anti-miR combination therapy [11]. Recently, many studies have investigated the biology of miR in Ewing sarcoma. The purpose of this brief report is to summarize the results of these studies and discuss the insights they have provided for the etiology of the disease and the potential options for subdivision and treatment of improved disease.

MicroRNAs in EWS/Fli1-Driven Oncogenesis

Most etiologies of Ewing sarcoma are caused by EWS / Ets fusion neoplastic proteins. It results from recurrent chromosomal translocations and is required for tumorigenesis [12, 13, 14]. The EWS / Ets fusion, where EWS / Fli1 is most common, is composed of the amino terminus of the EWS gene and the carboxy terminus containing the DNA binding domain of the Ets transcription factor gene. Transcriptional activity, including both activation and inhibition, is central to the carcinogenic effects of EWS / Ets [14, 15]. Since transcription and processing are important mechanisms that regulate intracellular miR levels [3, 4, 5], EWS / Ets fusion affects miR expression in Ewing sarcoma, resulting in miR mirror execution. It was reasonable to assume that it would contribute. Overview of EWS / Ets-led carcinogenic programs. EWS / Ets controlled miR identification and characterization are performed by several groups. Van et al. [16] depleted EWS / Fli1 in five different Ewing sarcoma cell lines using transient siRNA-mediated knockdown. Next, multiplex RT-between controls and EWS / Fli1-depleted cells, and between 5 Ewing sarcoma patient tumors and mesenchymal stem cells (MSC, presumed Ewing sarcoma-derived cells) from 6 different individuals. We compared miR levels using the qPCR platform. This approach identified 15 up-regulated miRs and 14 down-regulated miRs in all comparison groups. MiR-145 was the most consistently modified miR, with reduced EWS / Fli1 depletion and under expression compared to MSC for Ewing sarcoma. In support of its role in tumor suppression, the authors have shown that substitution of miR-145 results in inhibition of scaffold-independent proliferation of Ewing sarcoma cells. In addition, they show direct suppression of EWS / Fli1 by miR-145, suggesting the presence of a miR-mediated positive feedback loop that increases intracellular

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EWS / Fli1 protein levels. A similar feedback loop was developed by Riggi et al. [17], explained in more detail below. Subsequent studies have shown that another EWS / Fli1, miR-708, downregulates the miR involved in Ban et al.'S study. It has been shown to regulate the response of Ewing sarcoma to chemotherapy [18]. McKinsey et al. [19] attempted to stably knock down EWS / Fli1 in Ewing sarcoma A673 cells by examining changes in miR levels using a lentivirus-delivered shRNA and a miR microarray platform. This approach identified 29 upregulated miRs and 31 downregulated miRs in EWS / Fli1 depletion. They focused on groups of miRs that were upregulated after EWS / Fli1 knockdown (miR 22, 100, 125b, 221/222, 27a, and 29a), and these levels of miR were particularly relevant for EWS / Fli1 operations shown to be related. EWS / Fli1 depletion due to different shRNA and ectopic EWS / Fli1 expression in heterologous fusion negative cell lines, and these miRs are underexpressed in Ewing sarcoma cell lines compared to MSC. In terms of function, the authors showed that forced expression of these miRs inhibited the proliferation of A673 cells and a subset of miRs targeted components of IGF signaling. These studies suggest that suppression of selected miRs promotes EWS / Fli1-induced carcinogenesis by enhancing IGF pathway activity.

Many studies provide evidence to support the MSC origin of Ewing sarcoma [20, 21]. Therefore, an alternative approach to identify pathogenic miRs, including those caused by EWS / Fli1 in Ewing sarcoma, is to compare miR expression profiles between Ewing sarcoma and MSCs. Such an approach was proposed by De Vito et al. [22]. They identified 11 enriched and 24 depleted miRs in two Ewing sarcoma cell lines (A673 and TC252) compared to MSC. The depleted miR contained several members of the let-7 family that were previously shown to be tumor suppressor in other cancers. The authors show that EWS / Fli1 directly suppresses the expression of let-7a and that forced replacement of let-7a partially inhibits the growth of Ewing sarcoma tumor xenografts by regulating HMGA2 levels. First, some miRs (shown in bold) were identified in multiple studies, but many miR changes were specific to a particular study. Differences between Ban et al. S EWS / Fli1-dependent expression profiles [16] compared to that of McKinsey et al. [19]. There are several possible explanations. First, the use of temporary EWS / Fli1 depletion by Ban et al. In contrast to the stable depletion used in the other two studies, miR accumulation can occur immediately downstream of fusion tumor proteins. Alternatively, Ban et al. Simultaneous comparison across multiple cell lines and tumors, as described by. It may have imposed a very strict filter that eliminates the detection of some miR changes. Finally, some differences can be explained by the different controls and miR profiling platforms. Differences in profiling platforms may also explain some of the differences between McKinsey et al. Changes in the identified miR. Studies have shown that the same cell line (A673) and the general approach (stable EWS / Fli1 knockdown) were used. However, different controls, shRNA, culture conditions, and the exact depth of EWS / Fli1 knockdown indicate additional variables. Considering the differences between studies using a similar experimental approach (EWS / Fli1 depletion), McKinsey et al. S more diverse approach (EWS / Fli1 depletion) and De Vito et al. (Ewing sarcoma cell line and MSC profiling). Profile similarity between these studies suggests that EWS / Fli1 depletion may result in an MSC-like miR profile, as observed in the gene expression profile [23]. This seems to provide further evidence that MSCs or closely related cells may be of Ewing sarcoma origin. Other notable trends apparent from a comparison of cross-sectional studies of miR changes include fairly consistent upregulation of members of the paralogous 17-92a, 106b-25, and 106a-363 oncomiR clusters and miR-145 includes down regulation. Most biological effects of EWS / Fli1-related miR changes identified in the profiling studies above are awaiting characterization.

MicroRNA Expression and Disease Prognosis

Nakatani et al. [24] examined the potential role of miRs as predictive biomarkers in Ewing Sarcoma. In this investigation, global miR microarray profiling was performed on 34 primary Ewing Sarcoma tumors, comparing the expression profiles of patients with early relapse (median time from diagnosis 14 months, range 2–29 months) to those without clinical relapse (median follow-up 139 months, range 26–217 months). This analysis identified five miRs (34a, 23a, 92a, 490-3p, and 130b) that were significantly associated with both event-free and overall survival. In further analyses, low levels of miR-34a emerged as a particularly robust predictor of early relapse. In functional studies, the authors showed that miR-34a inhibits anchorage-independent growth of Ewing Sarcoma cell lines, and sensitizes to vincristine and doxorubicin. Consistent with the established role of p53 as a regulator of miR-34a expression, miR-34a levels were found to be low in Ewing Sarcoma cell lines with p53 inactivating mutations. Moreover, one tumor with low miR-34a levels was found to have a p53 mutation. This study examined p53 status in only a small number of tumors (six total). A question of interest for future studies is the extent of overlap between inactivation of the p53 pathway and miR-34a downer gulation in Ewing Sarcoma tumors. On the one hand, miR-34a may emerge as a very useful surrogate marker of p53 pathway status, potentially independent of mechanism of p53 inactivation. Alternatively, miR-34a may identify a new subgroup of patients with poor prognosis.

Conclusion

Studies of miR biology in Ewing sarcoma have been performed in the context of EWS / Fli1 co-fusion. It will be interesting to determine how miR expression and function differ in the context of other less common EWS / Ets fusions recently discovered, as well as the more diverse non-EWS / Ets fusions will miR-based therapies reach the clinic. As with all new concepts and methods, only time and more rigorous scientific knowledge will teach. Many interesting unanswered questions remain. A great deal remains to be learned about the mechanisms responsible for altered miR expression in Ewing Sarcoma. Similarly, the biology of individual miRs with altered expression patterns remains largely uncharacterized. Particularly intriguing is the role of miRs like miR-21 and miRs-221/222, identified as upregulated and pro-oncogenic in most malignancies, but observed to be downregulated in most profiling analyses of Ewing Sarcoma. Further, to date, studies of miR biology in Ewing Sarcoma have been carried out in the context of the common EWS/Fli1 fusion. It will be of interest to determine how miR expression and function differ in the context of the other, less common, EWS/Ets fusions, as well as the more divergent non-EWS/Ets fusions discovered recently. Will miR-based therapies make it to the clinic? As with all new concepts and methodologies, only time and more rigorous science will tell.

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Conflict of Interest

None

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