MiRNA in Rhabdomyosarcoma

Subjects: Pathology

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Rhabdomyosarcoma (RMS), the most common soft tissue sarcoma of childhood and adolescence, is a rare but aggressive malignancy that originates from immature mesenchymal cells committed to skeletal muscle differentiation. Although RMS is, generally, responsive to the modern multimodal therapeutic approaches, the prognosis of RMS depends on multiple variables and for some patients the outcome remains dismal. Further comprehension of the molecular and cellular biology of RMS would lead to identification of novel therapeutic targets. MicroRNAs (miRNAs) are small non-coding RNAs proved to function as key regulators of skeletal muscle cell fate determination and to play important roles in RMS pathogenesis. The purpose of this review is to better delineate the role of miRNAs as a biomarkers or functional leaders in RMS development, so to possibly elucidate some of RMS molecular mechanisms and potentially therapeutically target them to improve clinical management of pediatric RMS.

Keywords: miRNA ; Rhabdomyosarcoma

1. Introduction

As miRNAs play a crucial role in the development and progression of RMS, the possibility to exploit these molecules as new therapeutic targets in this pediatric tumor should be considered (Figure 1). To this matter, miR-378 over-expression was functionally demonstrated to cause changes in apoptosis, migration and viability through IGF1R down-modulation. Moreover, replacement of miR-378a-3p induces cytoskeleton organization as well as modulation of muscle protein, such as MyoD1, MyoR, desmin and the myosin heavy chain [1]. MiR-183 knockout guinea pigs showed a reduction in tumor cell migration in vitro and stimulation of phosphatase expression in the tumor suppressor gene and tensin homolog (PTEN), which in turn favored the expression of early growth response 1 (EGR1), thus, strengthening the repression of cell migration [2]. Therefore, miR-183 plays an oncogenic role by targeting two tumor suppressor genes, EGR1 and PTEN and miRNA deregulation is crucial to the development of several types of tumors. As for miR-9a, is able to inhibit cell migration and acts directly on E-cadherin [3] .

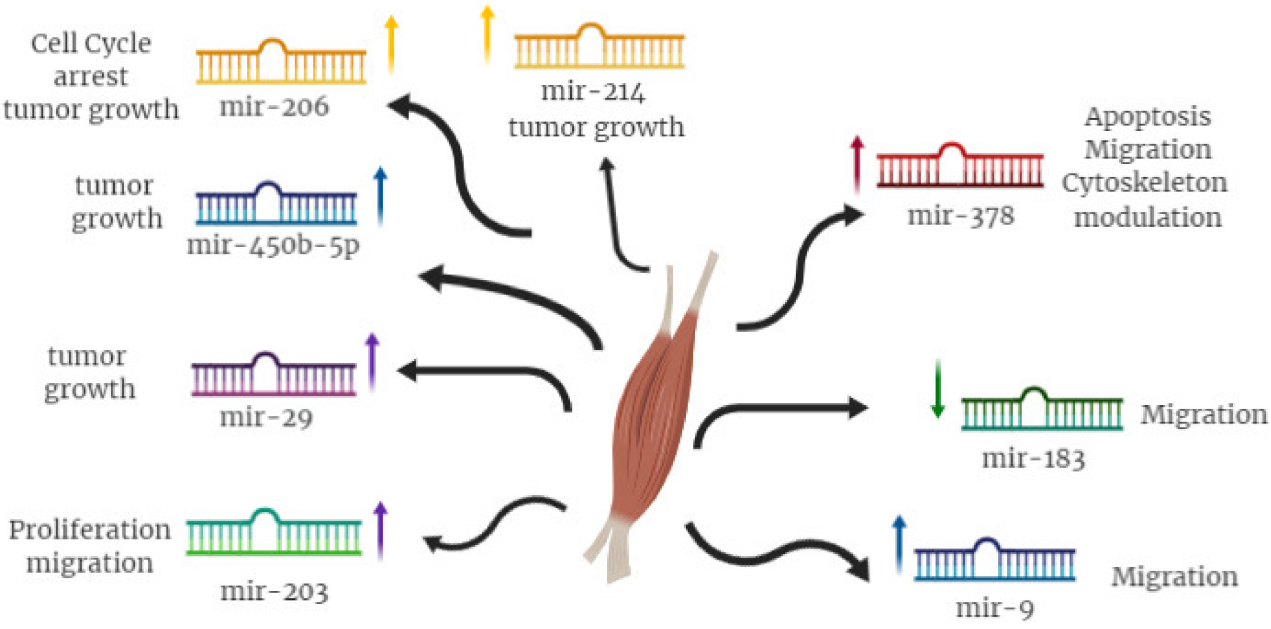

Figure 1. miRNAs modulation in RMS carcinogenesis.

2. MiRNA as Functional Players in RMS

To this regard, several approaches that up-regulate or down-regulate miRNAs have been used to characterize and identify the miRNAs involved in the RMS, demonstrating significant efficacy in the treatment of the pathogenesis of RMS following intravenous administration in vivo [4]. In particular, two pre-clinical studies have shown that ectopic expression of miR-206 by lentiviral vectors leads to cell cycle arrest and myogenic differentiation of RMS cells, preventing cell growth in vivo, thanks to inhibition of oncogene expression c-MET[5][6] . Furthermore, experiments with miR-183 knockdown mice led to significant reductions in tumor migration through the direct promotion of EGR1 expression, regulator of cell migration [2] . Re-expression of miR-203 in RMS cells inhibits their proliferation and migration and promotes terminal myogenic differentiation by acting directly on p63 and leukemia inhibitory factor through JAK/STAT (Janus Kinases/Signal Transducer Activator of Transcription Protein) pathway modulation [7] . miR-29 re-expression in mouse model of RMS inhibited tumor growth through stimulation of differentiation mechanisms, suggesting a tumor-suppressor role for this miRNA . Furthermore, in some studies, RMS growth and proliferation were significantly arrested by miR-450b-5p, strictly regulated by TGF-β1[8]. Huang et al. demonstrated that overexpression of miR-214 was able to inhibit RMS tumor growth both in vitro and in vivo and induced myogenic differentiation by down-modulation of N-Ras [9]

A major weakness of miRNAs modulation studies in RMS is the employment of only commercially available RMS cell lines for in vitro approaches without a further in vitro validation with primary RMS cell lines generated from patients' surgical specimen. An innovative way to bypass in vitro cell cultures could be the generation of in vivo models such as RMS Patients Derived Xenografts (RMS-PDXs). To date, few works reported the generation of RMS-PDXs, but none of them analyzed the potential of miRNAs in vivo in RMS development or for therapeutic purposes. Most of the functional studies did not consider the microenvironment role in RMS development that could influence cancer cells behavior and aggressiveness. Infiltrating immune cells have a critical and essential role in supporting tumor growth and this aspect should be also investigated to identify novel potential therapeutic targets for RMS management. The generation of innovative therapeutic agents combined miRNAs mimic or inhibitor with liposomes or nanoparticles, which could be a compelling challenge for RMS treatment for the next years. Although all reported data suggests a probable therapeutic role of miRNAs in RMS, unfortunately, the lack of pre-clinical data leaves unexplored such a critical issue that holds great clinical potential for this pediatric disease.

The publication can be found here:https://www.mdpi.com/1422-0067/20/22/5818/htm

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