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REVIEW ARTICLE

Dissecting the functional role of microRNA 21 in osteosarcoma

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Abstract

Osteosarcoma (OS) is considered to be a malignant bone tumour that mainly affects the long bones, but it is also involved in other bones of the body. Currently, surgery and chemotherapy have achieved some response to patients with OS, but they are not increasing the survival rate as well as treatment options. Researchers made lot of drug options for OS, but yet, no treatment is existing in sight for the disease and needs a new insight into the molecular and signaling pathways for the disease. Now, it is necessary to develop a novel and alternative strategy for the prognosis, diagnosis and treatment options for OS. MicroRNAs (miRNAs) are a small non-coding RNA, and their size ranges from 18 to 22 nt in length. In the nucleus, miRNAs originate and transcribe into primary transcripts and later cleaved to produce stem loop-structured precursor nucleotides. microRNA 21 (miR-21) is considered to be a trivial marker for many diseases and has been upregulated in many cancers. Moreover, it plays a main role in proliferation, migration, invasion and apoptosis. miR-21 and its associated pathways are very important and play a critical role in the pathogenesis of OS and are considered to be a biomarker and a therapeutic target for OS. To our knowledge, there is no paper that demonstrates the responsibility and the role of miR-21 in OS and the number of studies related to miR-21 in OS is spare. Therefore, the main aim of this paper is to give an outline of the recent clinical investigation and importance of miR-21 in OS. It has been suggested that the up- and downregulation of miRNAs plays a crucial role in the pathogenesis and progression of OS. Normally, miR-21 was found to be upregulated in OS; however, we summarize the clinical relevance and the recent research findings associated with miR-21 in OS.

Introduction

Osteosarcoma (OS) is considered to be a malignant bone tumour that mainly affects the long bones, but it is also involved in other bones of the body [1]. It is the most frequent bone cancer in children and as well as in young adults [2]. It has been suggested that OS emerges basically from mesenchymal stem cells that undergo aberrant alterations in the cell differentiation stages, leads to genomic instability, loss of heterozygocity and finally ends with tumour formation [2, 3]. Currently, surgery and chemotherapy have achieved some response to patients with OS, but they are not increasing the survival rate as well as treatment options [4]. Researchers made lot of drug options for OS, but yet, no treatment is existing in sight for the disease and needs a new insight into the molecular and signaling pathways for the disease. Now, it is necessary to develop a novel and alternative strategy for the prognosis, diagnosis and treatment options for OS.

MicroRNAs (miRNAs) are a small non-coding RNA, and their size ranges from 18 to 22 nt in length. In the nucleus, miRNAs originate and transcribe into primary transcripts and later cleaved to produce stem loop-structured precursor nucleotides [5, 6]. The precursor stem loop structure is then transported to the cytoplasm and further they are processed by an enzyme RNase III Dicer to produce mature miRNAs. Usually, mature miRNAs can recognize their cognate mRNA and bind its 3′ end of the untranslated region (UTR) for the post-transcriptional repression activity [7, 8, 9]. Until now, there are so many

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miRNAs that have been identified and characterized in human diseases. Recent reports have made extensive research on miRNAs and suggested that they play an important role in both a suppressive and promoting role in cancer metastasis [10]. In general, it is elevated in many diseases, i.e. cancer, diabetes, hypertension, cardiovascular disease, etc. [11]. Moreover, the miRNA–target gene relationship disruption may lead to several complications like tumour formation, metastasis and drug resistance [11, 12]. Furthermore, it has been proven that malignancies associated with miRNAs have been frequently found in the fragile sites and the genomic region, so it is very important to have extensive studies on miRNAs and their involvement in cancer progression.

microRNA 21 (miR-21) is considered to be a trivial marker for many diseases and has been upregulated in many cancers. Moreover, it plays a main role in proliferation, migration, invasion and apoptosis. hsa–miR-21 originated from chromosome 17q23.2 immediately to the vacuole membrane protein 1 (VMP 1) gene [13–15]. It has been documented that miR-21 is considered to be an oncogenic miRNA, which can bind to 3′ UTR of verities of tumour suppressor genes, such as phosphatase and tensin homologue (PTEN), tropomyosin 1 (TPM1) and programmed cell death protein 4 (PDCD4) to induce tumour and overexpression in tumour cells [16, 17, 18]. Interestingly, anti-miR-21 mediated inhibition of miR-21 in tumour cells by inhibiting growth, induction of apoptosis and inhibiting cell proliferation. In cancer stem cells (CSCs), miR-21 plays an important role in regulating cell differentaiation and chemoresistance [19].

Recent research papers demonstrated that miRNAs have been widely involved in the essential role of OS progressions [20–22]. miR-21 and its associated pathways are very important and play a critical role in the pathogenesis of OS and are considered to be a biomarker and a therapeutic target for OS [23, 24].

A report mentioned that miR-21 acts as a prognostic marker for OS and creates the impression of being a major regulator in OS cells [25]. A systemic review and meta-analysis also shows that an elevated expression of miR-21 has been seen in OS [4]. From the above points, we can conclude that miR-21 plays a significant role in the development of OS. To our knowledge, there is no paper that demonstrates the responsibility and the role of miR-21 in OS and the number of studies related to miR-21 in OS is spare. Therefore, the main aim of this paper is to give an outline of the recent clinical investigation and the importance of miR-21 from a PubMed-based article search related to the OS. It has been suggested that the up- and down regulation of miRNAs are associated and play a crucial role in the pathogenesis and progression of OS [26, 27]. Normally, miR-21 was found to be upregulated in OS; however, we summarize the clinical relevance and the recent research findings associated with miR-21 in OS.

Involvement of miR-21 in OS

A study by Zhang et al. [28] suggested that miR-21 and its associated pathways, including the X-inactive specific transcript (XIST) and PDCD4 might be a biomarker for OS. In this study, they indicated that XIST is considered to be a tumour suppressor and miR-21-5p interacted with XIST by directly targeting the miRNA-binding site in the XIST sequence, concluded that the above-said pathway is important for OS pathogenesis and might provide a new route for therapeutic targets. Another recent study reported that patients with OS show a significantly higher expression level of miR-21 than the normal control samples, before and after the chemotherapy that the serum levels were correlated with miR-21 expression and suggested that after the chemotherapy, the target genes for miR-21 significantly upregulated and the 5-year survival rate was relatively higher after surgery, so miR-21 may be considered as a biomarker for OS [24]. It has been suggested that miR-21 significantly shows higher expression in OS tissues compared with adjacent tissues and suppressed the apoptosis, but improves the cell viability and survival rate. Interestingly, a recent report suggested that LncRNA neuroblastoma-associated transcript 1 (NBAT1) suppresses the expression of miR-21 in OS and also targets the miR-21-associated genes in OS [29]. Molecular characterization of OS reveals that miR-21 has played an important role in OS metastasis with its target genes [30].

It has been reported that in OS tissue, miR-21 is highly expressed when compared with the adjacent tissues, so we can conclude that elevated expression of miR-21 is seen in OS [31]. A report by Ren et al. [32] suggested that miR-21 has played an important role in tumour progression and its qRT-PCR results indicated that miR-21 expression in tumour tissues is strongly elevated compared with the adjacent corresponding non-cancerous bone tissue. Furthermore, miR-21 upregulation is associated with poor clinicopathological characteristics and it may be used as a prognosis marker for OS. Interestingly, PTEN is considered as a target mRNA for miR-21 and it can activate the PI3K/Akt pathway by suppressing PTEN, suggesting that miR-21 plays an active role in OS and it can predict the occurrence and development of OS [33]. Recent reports show that overexpression of miR-21 has been seen in solid tumours and involved in the regulation of drug-induced resistance and it may serve as a potential candidate biomarker for OS [26, 27]. Figure 1 represents the role of miR-21 in OS.

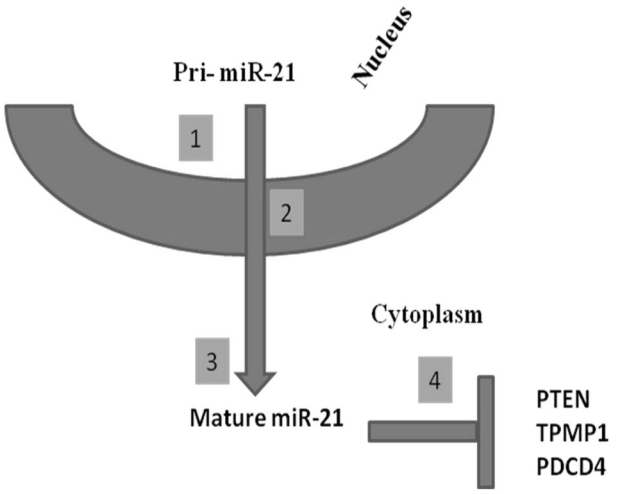

Fig. 1 This figure shows the miR-21 regulation in the cells

Clinical perspective and future directions

Recently, non-prot-coding RNAs such miRNAs play a vital role in the regulation of various genes responsible for tumour formation. It has been noted that all signal transduction pathways are stimulated or suppressed by plenty of miRNAs in the cells and miRNAs associated with their cognate target genes can modify the gene-regulating pathways. Clinically, the current treatment options for OS mainly depend upon the drugs and pathophysiology of the disease progression. Unfortunately, the genetic and molecular profiles were not considered while treating the patient. OS is one of the most common human primary malignancies in all age groups of people; interestingly, noninvasive biomarkers are emerging to detect an early stage for increasing the survival rate and determining the treatment option. miRNA is also considered as a noninvasive biomarker for early detection and it may open the way for treatment options for OS. Interestingly, miR-21 has been proved as an emerging biomarker for many diseases, including OS [34], but the number of studies related to OS is very limited and we need more investigation to prove that miR-21 is a strong biomarker and a therapeutic option for OS. In view of the fact that miR-21 is upregulated in OS, its distinctive molecular signatures can be used as prognostic, diagnostic and therapeutic targets. Repeated evidences suggested that miR-21 is a significant oncogene, which plays an important role in the regulation of OS. It has been observed that miR-21 upregulations enhance tumorigenicity in OS through activation of the associated genes and the additional signaling pathways. miRNA mimics, antogomiR or anti-miRNA oligonucleotides (AMO) coupled with locked nucleic acid (LNA) can be used to block the miRNAs in the cells [6, 10, 12]; however, we need further preclinical and clinical trials to prove the above concepts. At various doses of AMO, 2-O-methyl modification gave an effective inhibition of miRNAs in cell culture and xenograft mouse models [35]. However, further experimental validation is necessary for the above investigations in order to demonstrate that AMOs can function as therapeutic agents against OS and it is, therefore, significant to have future functional studies for miR-21 in OS.

Conclusions

In general, an aberrant expression of miRNAs is well characterized to play a role in the initiation and progression of various malignancies. More than 1000 miRNAs have been identified through bioinformatics and biological studies. From the above points, we can conclude that miR-21 is highly unregulated in OS metastasis. Moreover, molecular characterization of miR-21 in OS reveals that it can be the most challenging biomarker for OS and it may useful to prognosis, diagnosis and to find out the therapeutic drugs for OS. Inhibition of miR-21 may serve to reduce the progression of OS and it is an excellent tool for the treatment of diseases. However, this requires validated and more studies. In addition, more investigation will determine the future use and clinical application of miR-21 in this disease.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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