Journal of Clinical & Experimental Pathology

Ingrid, J Clin Exp Pathol 2022, 12:5

Commentary Open Access

The Biological Functions of miRNAs in the Development of Osteosarcoma

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Received: 21-Oct-2022, Manuscript No. JCEP-22-82915; **Editor assigned:** 24-Oct-2022, PreQC No. JCEP-22-82915 (PQ); **Reviewed:** 09-Nov-2022, QC No. JCEP-22-82915; **Revised:** 17-Nov-2022, Manuscript No. JCEP-22-82915 (R); **Published:** 24-Nov-2022, DOI:10.4172/2161-0681.22.12.422.

Citation: Ingrid N (2022) The Biological Functions of miRNAs in the Development of Osteosarcoma. J Clin Exp Pathol. 12: 422.

About the Study

The most frequent malignant bone tumour in children and adolescents is osteosarcoma (OS), which develops from early mesenchymal cells. Long bones' metaphyses, particularly those in the distal femur, proximal tibia, and proximal humerus, are where osteosarcoma most frequently develops. The majority of OS patients have discomfort and edoema in the afflicted region. The 5-year survival rate for patients with no metastases might be between 60% and 70% because to surgical resection, combination chemotherapy, and targeted radiation. The 5-year survival percentage for OS patients with metastases or recurrences, however, is just 10% to 20% since metastases and recurrences frequently have a poor prognosis.

Osteosarcoma has a high malignant grade, micro-lesion metastasis is probable in the diagnosis, and lung tissue is a common metastatic location. Simultaneously, osteosarcoma cells might develop resistance to numerous chemotherapeutic drugs during therapy, creating a big issue for osteosarcoma clinical management. Although overall survival is universally recognized as the gold standard in clinical research when assessing prognostic information or measuring treatment effects, the complexity of cancer death, including invasion, recurrence, and metastasis, still limits the practicality and reliability of OS in estimating cancer progress and prognosis. Furthermore, Positron Emission Tomography/Computed Tomography (PET/CT), a modern technology extensively utilized in clinical practice, showed greater accuracy, sensitivity, and specificity in the diagnosis of osteosarcoma.

The family of endogenous non-coding RNAs known as microRNAs (miRNAs) ranges in length from 19 to 25 nucleotides. They primarily control gene expression to carry out their biological tasks. Different forms of cancer are linked to altered miRNA expression, and these defective miRNAs frequently act as oncogenes or tumour suppressors throughout the genesis and spread of cancer. As a result, efforts can be made to enhance the expression of aberrant miRNAs by preventing the function of miRNAs that are overexpressed in cancer or by increasing the quantity of the downstream specific products of miRNAs that are underexpressed through a variety of pathways, thereby preventing the onset and spread of cancer.

The production and biological functions of miRNAs

The majority of miRNAs are created using the normal miRNA biogenesis route. MicroRNA genes are typically expressed as single transcription units, and mature miRNAs are synthesized in two phases, nuclear and cytoplasmic synthesis, which necessitates the participation of several enzymes. The majority of miRNAs are transcribed by RNA polymerase II in the nucleus, creating Primary miRNAs (pri-miRNAs) that encode miRNA sequences in a "hairpin" structure. The Drosha-DGCR8 complex excises pri-miRNAs in the nucleus to create precursor miRNAs (pre-miRNAs) with a "hairpin" shape. The pre-miRNAs are subsequently translocated to the top of the hairpin, where they generate precursor miRNAs (pre-miRNAs) with a "hairpin" structure. The transporter protein Exportin-5 subsequently transports the pre-miRNAs to the cytoplasm.

The double-stranded RNA (dsRNA) endoribonuclease/Transactivation Response (TAR) RNA Binding Protein (DICER/TRBP) complex binds to pre-miRNAs in the cytoplasm and cleaves the hairpin to create a complementary RNA duplex. While the other chain is destroyed, one of the nucleotide chains forms the miRNA-RISC complex by preferentially binding to the RNA-Induced Silencing Complex (RISC) including the Argonaut (Ago) protein. The local thermodynamic stability of the miRNAs has a significant impact on the strand choice, as duplex-RISC prefers to load onto the less thermodynamically stable 5′ end. The fact that miRNAs often start with uracil and the presence of mismatches and bumps in miRNA duplexes, which facilitate the loading of miRNA strands into RISC, both contribute to this thermodynamic difference.

Finally, Argonaut proteins direct the miRNA strand to the 3′-Untranslated Region (3′-UTR) of the mRNA target sequence and allow it to connect to the RISC. The structural properties of the 5′-UTR in mRNA, including the upstream UTR, secondary structure, start codon, Open-Reading Frame (ORF), and ribosome binding sites, control translation efficiency in the middle. Although the majority of mRNA transcription regulation occurs in the 5′-UTR, the 3′-UTRs of mRNAs play an essential role in the posttranscriptional control of gene expression due to the presence of cis-acting regions and interactions with miRNAs. It is generally accepted that miRNAs inhibit gene expression by interacting with the 3′-UTR sections of their target mRNAs. This alters a variety of biological processes, including growth, migration, and angiogenesis. Additionally, the 3′-UTR of mRNA provides signals for terminal processing, and its AU-rich region and miRNA targeted binding area control translational regulation of gene expression. Additionally, miRNA expression is noticeably dysregulated in cancer, according to several reports. Therefore, any alterations in miRNAs have the potential to target certain domains, such as the coding area of mRNA domains, which operate as binding sites and cause the miRNA to become oncogenic or tumour suppressor. MiRNAs can be produced outside the cell and may play an important role in intercellular communication. Extracellular miRNAs are found in vesicles, including apoptotic vesicles and exosomes, or attached to RNA-binding proteins like AGO and HDL.