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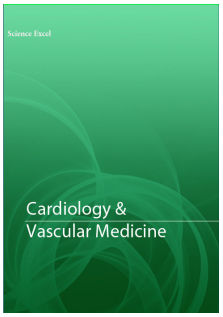

Mitochondrial Dysfunction in Osteosarcoma Patients

Daigo Hirao[1], Adil Maqbool[4], Takehito Sugasawa[2], AKM Shaharul Islam[3], Arifur Rahman[4], Farzana Sohael[4], Chishimba Nathan Mowa[4], Nobutake Shimojo[2], Subrina Jesmin[1,2,4]

[1]Hirao Cardiovascular Clinic, Chiba, Japan
[2]Faculty of Medicine, University of Tsukuba, Tsukuba, Japan
[3]TMSS Medical College and Hospital in Bogra, Bangladesh
[4]Health and Disease Research Center (HDRCRP), Bogra, Bangladesh

Correspondence
Dr. Daigo Hirao MD
Hirao Cardiovascular Clinic, Chiba, Japan

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Abstract

This review aims to explore the relationship between mitochondrial dysfunction and osteosarcoma progression. Osteosarcoma, a highly malignant primary bone tumor, has long been linked to various metabolic alterations, including mitochondrial anomalies. Mitochondria, known for their roles in energy production, reactive oxygen species regulation, and apoptosis, are implicated in cancer pathogenesis. This paper consolidates evidence from multiple studies, highlighting how mitochondrial dysfunction contributes to osteosarcoma development, tumor growth, and metastasis. Findings suggest that abnormal mitochondrial functions—ranging from disrupted energy metabolism to metabolic reprogramming—significantly impact tumor progression. Despite these insights, challenges persist in establishing a direct causal relationship. The review identifies potential therapeutic strategies targeting mitochondrial pathways and emphasizes the need for further studies to clarify mechanisms linking mitochondrial dysfunction and osteosarcoma.

Introduction

Osteosarcoma (OS) is one of the most aggressive primary bone cancers, primarily affecting children, adolescents, and, to a lesser extent, the elderly and canines [1]. As an invasive neoplasm, OS typically originates in the metaphysis of long bones, such as the proximal tibia, humerus, and femur, areas characterized by rapid bone growth [2]. Despite advancements in cancer treatment over the past four decades, improvements in OS survival rates have remained limited [3].

OS exhibits a strong propensity for early metastasis, further complicating prognosis and management. Two peak incidences of OS have been identified: one during childhood and adolescence (ages 5-24) and another in later adulthood, after 60 years [3]. The mortality rate is significantly influenced by factors such as tumor location, tumor size, and proximity to vital organs, as well as treatment modalities like early diagnosis, chemotherapy, total tumor resection, and radiotherapy [4]. Biomarkers such as serum alkaline phosphatase levels have also been identified as critical factors in determining prognosis both pre- and post-surgery [4].

Mitochondria, often referred to as the "powerhouses" of the cell, play essential roles beyond energy production, contributing to processes like calcium homeostasis, redox regulation, and programmed cell death [5]. Given these pivotal functions, mitochondrial dysfunction can have a profound impact on cellular metabolism and disease progression, including oncogenesis [5]. In the context of OS, mitochondrial abnormalities have been linked to altered cell death mechanisms, shifts in energy metabolism, and increased production of reactive oxygen species (ROS), which collectively influence tumor growth and metastasis [5].

Despite the clear involvement of mitochondrial pathways in cancer biology, the exact role of mitochondrial dysfunction in OS progression remains underexplored. Several studies have suggested potential links between mitochondrial alterations and OS, particularly through processes like Aminoimidazole Carboxamide Ribonucleotide (AICAR)-induced mitochondrial apoptosis [6]. However, establishing a direct causal relationship between mitochondrial dysfunction and OS progression has proven challenging [7].

This review aims to synthesize existing knowledge on the role of mitochondrial dysfunction in OS development and progression. By examining key metabolic pathways, genetic alterations, and mitochondrial dynamics, this study seeks to

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provide a comprehensive understanding of the mechanisms through which mitochondrial dysfunction may contribute to OS. Additionally, the review highlights potential therapeutic targets within mitochondrial pathways, which could lead to innovative treatment strategies for OS patients.

Osteosarcoma Prognosis in Relation with Mitochondria Dysfunction

Mitochondria are well-established as the primary energy providers within cells, playing a crucial role in sustaining biological functions. Beyond energy production, they also regulate oncogenic signaling, impacting processes vital to cell survival and growth, including stem cell functions. Mitochondria facilitate energy metabolism through glycolysis and redox reactions, while also producing intracellular reactive oxygen species (ROS), which are key components of cellular metabolism [8].

In cancer biology, studies have consistently shown that mitochondrial metabolic pathways undergo significant reprogramming. This reprogramming is central to maintaining redox homeostasis and bioenergetics within cancer cells. One of the most notable phenomena in this context is the Warburg effect, characterized by increased glucose uptake and a preference for glycolysis over oxidative phosphorylation, despite adequate oxygen availability. This shift is considered an abnormal metabolic adaptation driven by cancer cells, with glycolysis becoming the predominant pathway for ATP production [9].

The proliferation of cancer cells is further accelerated by elevated levels of mitochondrial metabolite ROS. Similarly, excessive glutamine decomposition contributes to cancer cell growth, enhancing tumor development and metastasis. It has been hypothesized that abnormal mitochondria-regulated energy metabolism plays a significant role in the onset and progression of osteosarcoma. Currently, researchers are exploring the connection between mitochondrial energy dysregulation and disease metastasis [10].

Changes in Mitochondrial Function Connected to Osteosarcoma

Mitochondria has numerous functions to perform in order to keep the human body in proper condition. It participates in many processes like cell repair and homeostasis. When the mitochondria performs these functions, it can experience changes which affects the biological features. Some of those changes to features are morphological expansion and also contractions, as well as changes in the membranes potential. In addition, the mitochondrial density undergoes changes while the overall dynamics of the mitochondria is modified. Changes of this nature can affect at a cellular level to all the molecular mechanisms [11].

Generally, the mitochondrial function changes can be divided into two types: physiological and pathological changes. When normal conditions prevail from a physiological standpoint, it is the metabolic rate that influences the mitochondrial functions. In cases of high levels of metabolic activities, the amount of mitochondria reaches a range of 1,000 to 2,000/cell. The cells in question are liver cells as well as cardiac cells. If there is a rise in metabolism demands, these cells will increase the amount of mitochondria as an act of compensation. As a result, it fosters the cellular metabolic functionalities [12].

Any change that takes place pathologically to the mitochondrial function is referred to as mitochondrial dysfunction. The root cause is oxidative stress, exogenous stimuli and lastly programmed cell death. Mitochondrial dysfunction materializes in the form of loss of membrane potential and ruptures in the mitochondrial membranes. Other than that, there are other indications like unusual shrinking of the mitochondria or even swelling. In an extreme case, excess amount of fusion can create a giant mitochondria. In the aftermath of mitochondrial dysfunction, we see the emergence of Osteosarcoma [13].

Metabolic Reprogramming in relation with Osteosarcoma

The tumor metabolism is complicated as a biochemical regulatory network. It is more so in the case of mitochondria-regulated tumor. Tumor cells begin proliferating once the mitochondrial functionality is subverted. There is a difference in energy requirement when that happens. However, the tumor cells are capable of adapting to the changes in that field as well as the overall environment. The condition that is created from this is called Hypoxia. In fact, it can also be termed as the tumor metabolic reprogramming. The phenomena can affect a number of stages in tumor's progression. When the tumor grows, it depends on glycolysis derived from the cytoplasm in the production of ATP. Through this process, the tumor gains energy [14]. In recent years, studies conducted reveal the energy characteristics depicted through the glycolysis ratio can be a reflector of the differentiation potential of the OS cells [15].

Table 1: Overview of Mitochondrial Changes in Osteosarcoma

Mitochondrial Alteration	Description	Impact on Osteosarcoma	Reference
Oxidative Stress	Increase in mitochondrial ROS production	Promotes tumor growth, gene mutation, and metastasis	[Selvarajah et al., 2010]
Dysfunctional Energy Metabolism	Shift from oxidative phosphorylation to glycolysis	Warburg effect, ATP production shifts to glycolysis	[Liberti & Locasale, 2016]
mtDNA Mutations	Point mutations, insertions, deletions in mtDNA	Contributes to cancer progression and therapeutic resistance	[Petros et al., 2005]
Mitochondrial Fission	Increased fission events leading to fragmented mitochondria	Correlates with aggressive tumor behavior, poor prognosis	[Kraus et al., 2021]
Glutamine Dependency	Shift in TCA cycle substrate from pyruvate to glutamine	Aids tumor growth under hypoxic conditions	[Fan et al., 2013]

Glycolysis Impact on Osteosarcoma

The human body heavily relies on glucose as the prime energy source. When cancer cells grow, the uptake of glucose increases and develops the path for positron emission tomography. The problem here is, glucose is hydrophilic whereas the cell membrane's main body remains hydrophobic. In order to transport glucose, it is vital to use the glucose transport proteins. The increase of glucose uptake by cancer cells, is a result of the aforementioned proteins overexpression. It is no surprise that the cancer cells in particular react positively to hypoxia.

The transporter proteins are termed as GLUT1 and GLUT3. Of the two, GLUT1 has an overexpression in the OS tissues and it is a significant factor for survival rate. Patients who have a high expression of GLUT1 in their system have a lower possibility of survival in comparison with those who have GLUT1 at standard level [16]. In addition, there is a negative correlation between the microvessel density values of osteosarcoma and the protein GLUT1 [17].

Role of Mitochondria Dysfunction

The Broad Institute Cancer Cell Lines Encyclopedia was used by experts to analyze 934 human cancer cell lines for the RNA-seq data [18]. Brefeldin A-inhibited guanine nucleotide exchange protein also known as BIG3 is present in the cell lines of OS at a higher amount than the usual bone tumors. It is worth noting that there is an up-regulation in the expression of BIG3 for tumors in comparison with corresponding regular tissues. As part of a study, the endogenous expression of BIG3 had been knocked down. The purpose was to see if BIG3 had a role in the proliferation of OS cells. It has been achieved with the help of siRNA in the MG-63 cells [18].

Mitochondria plays a key role in a number of processes like the amino acid metabolism, tricarboxylic acid (TCA) cycle along with the metabolism of nucleic acid [19]. To go with that, after some keen observation it has been revealed that the mtDNA of cancer cells undergo some mutations. There are also varying degrees of mutation in the nuclear genes belonging to the TCA cycle. Mutations of these two can lead to the remodeling of cancer cells [20].

Meanwhile, changes in the mitochondrial metabolic pathways contributes to mutations in the tumor suppressor genes. The outcome of these changes is the remodeling of cancer cells. For this reason, many studies have reached the conclusion that the metabolism reprogramming activities are key indicators of cancer [21]. Mitochondrial matrix is the host to the TCA cycle. In that cycle, a number of nutrients namely, glutamine, glucose etc. are used for generating ATP.

When normal circumstances prevail, the TCA cycle is fueled by pyruvate. However, the emergence of a hypoxic tumor microenvironment brings a shift resulting in the TCA cycle being fueled by glutamine [22]. Meanwhile, there are variations in the tumor's microenvironment as there are multiple factors such as, oxygen content, acidic circumstances and the oxidative stress prevailing in stromal cells as well as cancer cells. In its effort to grow, the cancer cells will use up these nutrients in quick order. The outcome which follows is nutrient deprivation as well as hypoxia.

While the Warburg effect states the affinity towards aerobic glycolysis, a large portion of cancer cells can manage an unharmed mitochondria [23]. Moreover, there have been energetic shifts occurring in the cancer cells between OXPHOS and glycolysis. During this time, the tumor's microenvironment provides the opportunity for ROS to become elevated and it originates due to mitochondrial dysfunction as well as other occurrences. Some of the other occurrences are oncogenesis and the dysregulation of enzymes. As cancer progresses, the condition of the tumor's microenvironment comes under risk for the mitochondria. The reason for that is the lower level of oxygen compared to the high level of oxidative stress. In addition, there is a restriction on the nutrient levels [24].

Genes and dynamics of mitochondria may undergo alterations as observed numerous times in cancer cells. To go with it, there are alterations in the mitochondrial activities and its content. The genome of mtDNA is known for having vulnerability as there is a lack of proper DNA repair systems. In addition, mtDNA is located close to the generation site for ROS. Mitochondrial dysfunction appears in the form of a vicious cycle when the oxidative stress is enhanced. The enhancement occurs under the influence of mtDNA mutation-mediated dysfunction of the mitochondria [25].

Changes in mtDNA can be of different kinds, for instance, insertions, point mutations and high amount of deletion to name a few. All three of them have been traced in cancer cells. A highly futuristic sequencing technique was used to analyze the changes in comprehensive mitochondrial genome. The result is that there is a strong link between the mtDNA content and certain clinical outcomes. Those specific outcomes are the ones where there is a link between low tumor mtDNA content and the adrenocortical carcinoma. It has also been found that the survival rate for these cases is on the lower side [26]. Moreover, these studies are further proof of the fact that tumors such as osteosarcoma have a presence of mtDNA mutations inside.

There are two types of mtDNA mutations present in the carcinogenesis. One is driver mutation and the other is passenger alteration. The presence of either can cause much problems [27]. Ratio of nonsynonymous to synonymous mutation of the mtDNA is represented as dN/dS ratio for the malignancies. This ratio is quite high when compared to a random expectation. It has been inferred that this high level of ratio for the mtDNA mutations reserve positive selection advantages. There is presence of heteroplasmy in the tumors and they are aided by mtDNA in the form of frameshift mutations as well as nonsense mutations. It is important to point out that the nonsense mutations is on the lower side in tumors which hold silent mutations of mtDNA [28].

The organelles known as mitochondria are constantly undergoing processes like fusion and fission. When fusion occurs, the mitochondrial connections stretch. In turn, the capacity of OXPHOS increases to compensate for the required energy level. The process of fusion mitigates the metabolic stress thereby maintaining the mitochondrial function. In addition, it decreases mitochondrial fragmentation [29]. Fusion of the mitochondria includes fusion of outer membrane along with mitofusin (MFN)1 as well as MFN2 and inner membrane having another fusion. It is achieved with the help of optic atrophy (OPA1).

Meanwhile, the mitochondrial membranes become fused when the GTPases are activated by the mitochondrial phospholipase D [30]. As for mitochondrial fission, it can be described as a successive procedure that is influenced by a number of factors. Some of the factors are the mitochondrial fission factor, mitochondrial dynamic protein of 51kD to name a few. The fission is responsible for a below par prognosis for several types of cancers. The role played by mitochondrial

fission is certainly a factor but its strength is yet to be fully determined. In some of the cases of renal clear cell carcinomas, the below par prognosis has been linked with the existence of a lower level of MFN2 expression [31].

Findings

Multiple studies have confirmed the presence of mitochondrial dysfunction in osteosarcoma, affecting various aspects of tumor growth, metastasis, and cellular behavior. Mitochondria, known for their critical roles in energy production, apoptosis regulation, and reactive oxygen species (ROS) management, exhibit altered functions in osteosarcoma cells. This dysfunction manifests in several forms, including metabolic reprogramming, increased ROS generation, and abnormal mitochondrial dynamics. These changes contribute to the aggressive nature of osteosarcoma, making mitochondria a potential focal point for therapeutic interventions.

In analyzing the link between mitochondrial dysfunction and osteosarcoma progression, a pattern of altered energy metabolism emerges as a key driver of tumor proliferation. Studies indicate a shift from normal mitochondrial oxidative phosphorylation to enhanced glycolysis, known as the Warburg effect. This shift enables rapid ATP production even in hypoxic tumor microenvironments, supporting cancer cell survival and growth. Elevated levels of ROS, resulting from dysfunctional mitochondria, further promote tumorigenesis by inducing DNA damage and activating oncogenic signaling pathways. These findings underscore the importance of targeting mitochondrial metabolic pathways to control osteosarcoma progression.

Additionally, mitochondrial DNA (mtDNA) mutations and copy number variations have been observed in osteosarcoma cells, providing insights into the genetic basis of mitochondrial dysfunction in this disease. The presence of both driver and passenger mutations in mtDNA suggests their potential role in the progression and metastasis of osteosarcoma. Abnormalities in mtDNA are often associated with impaired oxidative phosphorylation and increased reliance on glutamine metabolism, a characteristic feature of aggressive tumors. The identification of specific mtDNA alterations as biomarkers could aid in prognosis and therapy design. Aberrations in processes, like fission and fusion, have been linked to osteosarcoma progression, with increased mitochondrial fission correlating with poor prognosis. Therapeutic strategies aimed at restoring normal mitochondrial dynamics may thus offer a novel approach to managing the disease.

While changes occur in mitochondrial fission, there is a decrease in the mitochondrial filamentous network. In addition, mtDNA copy number also decreases at an alarming rate which can also be used in the prognosis for Osteosarcoma. This study dives into the possibility of targeting mitochondrial fission in order to salvage mitochondrial functionalities [32].

Possible Future Directions

Given the pivotal role of mitochondrial dysfunction in the progression of osteosarcoma, future research should focus on exploring specific mitochondrial pathways as potential targets for therapeutic interventions. One promising approach is to investigate the inhibition of metabolic reprogramming, a hallmark of osteosarcoma. Strategies that inhibit aberrant glycolysis or modulate mitochondrial oxidative phosphorylation could offer new therapeutic avenues. The effectiveness of glycolysis inhibitors or agents designed to restore mitochondrial oxidative functions warrants further exploration, as these interventions could alter tumor growth dynamics and improve patient outcomes.

Developing drugs that modulate key mitochondrial functions, such as inducing apoptosis or regulating reactive oxygen species, presents another viable direction. Therapeutic agents aimed at restoring mitochondrial integrity or enhancing mitochondrial biogenesis could be effective in reducing tumor aggressiveness. In addition, identifying and validating mitochondrial biomarkers in osteosarcoma may provide tools for early diagnosis and more accurate prognosis. Mitochondrial DNA mutations, copy number variations, and alterations in mitochondrial dynamics should be evaluated as potential biomarkers for tracking disease progression and treatment responses.

Research should also delve into the interactions between mitochondrial dysfunction and immune responses within the tumor microenvironment. Mitochondria significantly influence immune cell behavior, and understanding these interactions could refine existing therapies or lead to novel combinational approaches that incorporate immune-modulating agents. Exploring these immune-mitochondrial dynamics could enhance the efficacy of immunotherapy in osteosarcoma patients.

Integrating mitochondrial analysis into personalized medicine approaches for osteosarcoma could optimize treatment strategies tailored to the metabolic vulnerabilities

Table 2: *Mitochondrial-Targeted Therapeutic Approaches in Osteosarcoma*

Therapeutic Approach	Mechanism of Action	Effect on Osteosarcoma	Status	Reference
AICAR	Induces mitochondrial apoptosis	Promotes osteosarcoma cell death	Preclinical	[Lai et al., 2022]
Glycolysis Inhibitors	Inhibits key glycolytic enzymes (e.g., hexokinase)	Reduces ATP production, limits tumor growth	Clinical trials	[Liberti & Locasale, 2016]
mtROS Modulators	Regulates reactive oxygen species	Limits oxidative damage, inhibits cancer progression	Preclinical	[Hu et al., 2018]
mtDNA Repair Enhancers	Promotes mtDNA repair and integrity	Reduces mutation-driven tumor progression	Under investigation	[Yuan et al., 2020]
Mitochondrial Fusion Promoters	Enhances mitochondrial fusion and function	Mitigates mitochondrial dysfunction, improves prognosis	Preclinical	[Heine & Hood, 2020]

of individual patients. Personalized therapies, based on mitochondrial profiles, might improve treatment efficacy while minimizing adverse effects. Overall, a deeper understanding of the mechanisms linking mitochondrial dysfunction to osteosarcoma is crucial for translating these findings into clinical applications. Advancements in mitochondrial-focused therapies could significantly improve patient outcomes in this aggressive disease.

Conclusion

This review establishes that mitochondrial dysfunction plays a crucial role in the progression of osteosarcoma, influencing tumor growth, metastasis, and cellular survival. The intricate relationship between mitochondrial anomalies and osteosarcoma's aggressive behavior underscores the need for targeted therapeutic interventions that can modulate mitochondrial functions. While current findings indicate a strong association, establishing a direct causal link between mitochondrial dysfunction and osteosarcoma progression remains a challenge due to the complexity of tumor metabolism and microenvironmental factors. Future research should focus on identifying specific mitochondrial pathways that contribute to osteosarcoma development, with an emphasis on potential therapeutic targets like metabolic reprogramming, reactive oxygen species regulation, and apoptosis control. Advancements in understanding these pathways could lead to novel, mitochondria-focused treatment strategies, improving prognosis and survival rates in osteosarcoma patients.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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