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Literature Review: The Role Of Pyruvate Kinase M2 In Aerobic Glycolysis Of Cancer Cells: Mechanisms And Potential Inhibitor

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ABSTRACT

Cancer is defined as the uncontrolled growth of cells that can spread to other parts of the body, leading to significant health issues and affecting the quality of life patients. One hallmark of cancer is its ability to reprogram metabolism to support rapid cell proliferation, even under adverse conditions such as low oxygen levels. This article aims to explore how cancer cells predominantly utilize aerobic glycolysis, converting glucose into lactate, a process known as the Warburg Effect. This metabolic shift allows cancer cells to quickly generate energy and produce necessary biomass, including NADH, which is vital for maintaining redox balance and supporting continued proliferation. Pyruvate Kinase M2 (PKM2) is highlighted as a primary regulator of aerobic glycolysis in cancer cells. It facilitates the conversion of phosphoenolpyruvate (PEP) to pyruvate, which is crucial for lactate production. The low affinity of PKM2 for this conversion contributes to the metabolic advantages that cancer cells exploit. The review emphasizes the potential of targeting PKM2 as a therapeutic strategy for cancer treatment. Inhibiting PKM2 could disrupt the metabolic pathways that cancer cells rely on, with studies indicating that high doses of docosahexaenoic acid (DHA) can reduce PKM2 expression, presenting a promising direction for future research.

Keywords : Cancer, pyruvate kinase M2, aerobic glycolysis, inhibitors

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INTRODUCTION

The metabolic process in cancer cells to fulfill energy requirements is carried out through aerobic glycolysis. The conversion of glucose into lactate by cancer cells is a strategy to rapidly meet their energy demands, this phenomenon known as the Warburg Effect.[1] Energy metabolism in cancer cells is utilized to form new cells, necessitating a quick production of energy. Cancer cells also utilize the intermediate products of the aerobic glycolysis process for biomass synthesis. The biomass produced includes NADH, which can be used for one-carbon metabolism. This one-carbon product allows cancer cells to maintain redox balance, continued proliferation, preventing senescence and cell death.[2]

The occurrence of aerobic glycolysis in cancer cells is regulated by the expression of Hypoxia-Inducible Factor-1α (HIF-1α) via Phosphoinositide 3-Kinase (PI3K) signaling pathway. HIF-1α activation in cancer cells induces upregulation of Glucose Transporter 1 (GLUT1), Pyruvate Kinase M2 isoform (PKM2), Pyruvate Dehydrogenase Kinase 1 (PDK1), and Lactate Dehydrogenase (LDH). The key difference between normal cells and cancer cells in the aerobic glycolysis process lies in the activation of Pyruvate Kinase (PK), which involves distinct isoforms. In normal cells, the active isoform is Pyruvate Kinase M1 (PKM1), while in cancer cells, the main isoform that works is Pyruvate Kinase M2 (PKM2). PKM2 serves as a key enzyme involved in energy production, gene transcription, and carcinogenesis. It plays a crucial role in cancer cell glycolysis by catalyzing the conversion of phosphoenolpyruvate to pyruvate. Lactate is the primary end product of aerobic glycolysis in cancer cells. The Mammalian Target of Rapamycin (mTOR) regulates cellular functions, including protein synthesis, metabolism, and cell proliferation. mTOR functions as an upstream regulator of PKM2.[3]

In a study on esophageal carcinoma using immunohistochemical staining, it was found that the expression levels of mTOR and PKM2 in cancer cells were significantly higher compared to non-cancerous cells.[4] Activation or inactivation of mTOR leads to changes in PKM2 and HIF-1α expression during glycolysis. This indicates that mTOR regulates PKM2 through the downstream transcription factor HIF-1α in cancer cell glycolysis. PKM2 affects cancer metabolism, as it is known that mTOR downstream signaling induces HIF-1α activation, which, in turn, regulates PKM2. This review article aims to explore the role of PKM2 in the aerobic glycolysis of cancer cells.

WHAT IS CANCER?

Cancer is a disease characterized by the uncontrolled growth of tumor cells, accompanied by the spread of cancer cells, excessive utilization of the body's resources, changes in cellular metabolism, tissue damage, and the disruption of normal cell functions, which collectively disturb the body's overall homeostasis. This process leads to pain, organ dysfunction, and pathological conditions such as cachexia. In addition to its impact on physical health, cancer significantly affects the mental health of patients, disrupting their quality of life, family relationships, and social interactions. Each year, cancer causes the death of 10 million people worldwide, highlighting the severity of this disease. The economic

impact of cancer is substantial, encompassing direct medical costs, loss of productivity due to morbidity and premature mortality, and the emotional burden experienced by patients and their families. Global estimates indicate that the total economic cost associated with cancer exceeds 1 trillion USD annually.[5,6]

Cancer cells drive tumor growth and metastasis.[6] The Hallmarks of Cancer refers to a set of biological characteristics shared by almost all types of cancer cells, describing how these cells behave to support their growth, spread, and survival, as well as how they evade the body's defense mechanisms designed to stop or limit the growth of abnormal cells. This concept was first introduced by Hanahan and Weinberg in 2000 and has since evolved into a deeper understanding *of the molecular mechanisms underlying cancer*. [7,8] Fundamentally, cancer cells have the ability to modify mechanisms to bypass the normal regulatory controls of the body. For instance, they manipulate signaling pathways to sustain continuous proliferation in the absence of extrinsic signals that typically restrict cell growth. Moreover, cancer cells can avoid programmed cell death (apoptosis), which normally eliminates damaged or abnormal cells. Cancer cells also frequently reprogram their metabolism to support rapid proliferation, even under conditions of oxygen or nutrient deprivation. One of the important hallmarks of cancer is its ability to induce the formation of new blood vessels (angiogenesis) to meet its increased demand for nutrients and oxygen, as well as its capacity to spread (metastasize) to other parts of the body, causing further damage to surrounding organs and tissues. Additionally, cancer cells can adapt to the changing tumor microenvironment, such as low oxygen levels or the accumulation of metabolic waste, which would typically be lethal to normal cells.[8] By understanding the fundamental characteristics that enable cancer to grow and spread, researchers can design more targeted treatment strategies to address the essential biological mechanisms of cancer. The "Hallmarks of Cancer" serve as a guide for researchers and clinicians in discovering new approaches to combat this complex and deadly disease. To date, three well-established cancer treatments have been developed: surgery, chemotherapy, and radiotherapy. These treatment modalities aim to eliminate or attack cancer cells.[9]

In recent years, scientists have highlighted the critical role of the immune system in cancer. Cancer cells can avoid detection and destruction by the immune system through various mechanisms, including modifying their surface or activating immune checkpoint pathways. Both basic and clinical research on the tumor microenvironment, which comprises cancer cells, stromal cells, and immune cells, has demonstrated the significant role of antitumor immunity in cancer development and progression. As a result, cancer treatment now focuses not only on directly destroying cancer cells but also on strengthening or restoring the immune system's ability to recognize and eliminate cancer cells. Cancer immunotherapy has been reconsidered and recognized as the fourth modality of cancer treatment.[8,9]

SIGNALING PATHWAY OF CANCER

mTOR (mechanistic Target of Rapamycin) is a serine/threonine kinase activated by various oncogenic signals through the PI3K signaling pathway, regulating cellular functions such as protein synthesis,

metabolism, and cell proliferation.[10] The mTOR complex is divided into two distinct complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). Each complex consists of different protein components and phosphorylates distinct substrates. The mTORC1 inhibitor, rapamycin, has been widely used in research and therapy, allowing the functions and regulation of mTORC1 to be well characterized.[11] In contrast, mTORC2 is significantly less sensitive to rapamycin than mTORC1.

In addition to inhibition by rapamycin, the mTOR signaling pathway can also be suppressed by several genes, such as the tuberous sclerosis complex 2 (TSC2) and phosphatase and tensin homolog deleted on chromosome ten (PTEN). Loss or mutation of these genes can lead to the inheritance of cancer.[12] It is also known that mTORC1 plays a role in suppressing autophagy during metabolic processes.[13] mTOR is phosphorylated by Akt1 at Ser-2448, forming phospho-mTOR (p-mTOR), which regulates ribosome biogenesis and protein synthesis. mTOR is localized in both the cytoplasm and nucleus, and high expression of p-mTOR has been shown to reduce the response to cancer cell treatments.[14] HIF-1α is a downstream target of mTOR. HIF-1α is a key transcription factor that regulates cellular adaptation to hypoxia and can influence glycolytic metabolism under both hypoxic and normoxic conditions. Activated HIF-1α triggers the expression of glycolysis-related markers, thereby affecting the glycolytic rate in cancer cells. The activation of HIF-1α enhances cancer cell proliferation, contributing to the Warburg Effect. Conversely, the inactivation of HIF-1α can inhibit lactate production and reduce PKM2 expression in pancreatic cancer.[3]

AEROBIC GLYCOLYSIS MECHANISM

Aerobic glycolysis is a metabolic pathway that converts glucose into lactate, even in the presence of oxygen, commonly referred to as the Warburg Effect. During glycolysis in the cytoplasm process, one molecule of glucose is metabolized into two molecules of pyruvate through a series of enzymatic reactions. This process generates two molecules of ATP via substrate-level phosphorylation and produces two molecules of NADH. Under anaerobic conditions, the pyruvate produced would typically enter the mitochondria and proceed through the citric acid cycle (Krebs cycle) to be oxidized into CO_2 and H_2O, yielding a substantial amount of ATP. However, in aerobic glycolysis, despite adequate oxygen availability, pyruvate is converted into lactate by the enzyme lactate dehydrogenase (LDH). This conversion facilitates the regeneration of NAD+, enabling glycolysis to continue uninterrupted.[15,16]

At the cellular level, aerobic glycolysis functions to meet the energy and biosynthetic precursor requirements of the cell. In addition to generating two ATP molecules per glucose molecule, aerobic glycolysis also produces other metabolites essential for macromolecule synthesis. Some of these metabolites include amino acids, nucleotides, and lipids, which are necessary for cell division and growth. Aerobic glycolysis frequently happens in cancer cells, allowing rapid cell growth and division. This process is mediated by the upregulation of glycolytic enzymes, such as hexokinase, phosphofructokinase-1 (PFK-1), and pyruvate kinase, driven by transcription factors like hypoxia-

inducible factor 1-alpha (HIF-1α), which plays a critical role in adaptation to hypoxic conditions.[17,18] The formation of large amounts of lactate contributes to the acidification of the tumor microenvironment, which can enhance the invasive and metastatic capabilities of cancer cells. Additionally, lactate produced by cancer cells can be exported to the extracellular environment, where it acts as a signaling molecule regulating various cellular processes, including immune cell regulation.[16,19,20] In cancer cells, glycolytic enzymes such as hexokinase, phosphofructokinase-1 (PFK-1), and pyruvate kinase are often expressed at elevated levels, regulated by transcription factors like hypoxia-inducible factor 1-alpha (HIF-1α), which is activated under hypoxic or oxygen-deficient conditions.[19]

PYRUVAT KINASE ENZYME

The regulation of pyruvate kinase (PK) enzymes controls the glycolysis process in both normal and cancer cells. PK catalyzes the dephosphorylation of phosphoenolpyruvate (PEP) into pyruvate. PK exists in several isoforms, including PKM1 and PKM2, which are produced through alternative splicing of the PKM gene transcript. PKM1 is expressed in adult tissues, particularly in energy-demanding organs such as muscles and the brain, whereas PKM2 is expressed in certain differentiated tissues, including embryonic cells, stem cells, and cancer cells.[21] In normal cells, PKM1 forms a tetramer with a high affinity for PEP, allowing it to convert PEP into pyruvate more efficiently than PKM2, which forms a dimer in cancer cells.[22]

In 1956, Otto Warburg proposed that cancer cells have the ability to convert glucose into lactate to generate energy, even in the presence of sufficient oxygen. This phenomenon is known as aerobic glycolysis or the Warburg Effect. PKM2 is a critical enzyme in cancer cell metabolism and plays a key role in driving the Warburg Effect. During glycolysis, pyruvate is converted into lactic acid and adenosine triphosphate (ATP), which serve as the primary energy source to fuel the rapid proliferation of cancer cells. High PKM2 expression has been associated with increased cancer cell growth in pancreatic cancer, hepatocellular carcinoma, and colorectal cancer.[23,24,25]

REGULATION OF PKM2 IN AEROBIC GLYCOLYSIS OF CANCER CELLS

mTOR and PKM2 are critical signaling molecules in cancer cells. Immunohistochemical analysis of esophageal carcinoma revealed that high mTOR expression correlates with elevated PKM2 expression, both playing essential roles in regulating cancer cell glycolysis. PKM2 functions as the key enzymatic regulator of aerobic glycolysis, while the mTOR pathway plays a role in activating PKM2, thereby facilitating the glycolytic process in cancer cells.[4] mTOR activation pathways can affect PKM2 expression in pancreatic, prostate, and liver cancer cell cultures. The modification (knockdown) of PKM2 can significantly affect the glycolytic metabolism of cancer cells. Cells with knocked-down PKM2 exhibit higher glucose consumption and reduced lactate production compared to control groups. Lactate concentration tests reveal that altered PKM2 expression affects lactate production in cancer

cells. These findings suggest that high PKM2 expression enhances aerobic glycolysis, while low PKM2 expression inhibits the glycolytic process in cancer cells. Regulation of PKM2 expression induces changes in the aerobic glycolysis process.[4]

Inhibition of mTOR and p-mTOR was achieved by adding rapamycin to the cell culture medium. Western blotting analysis revealed that the expression of p-mTOR was significantly reduced after inhibition with rapamycin. Cancer cells with mTOR inhibited by rapamycin exhibited high glucose consumption and reduced lactate production compared to the control group.[4] This indicates that inhibition of the mTOR pathway leads to decreased lactate production, highlighting the role of mTOR in regulating glycolysis. In a separate group, PTEN gene knockdown was performed to activate mTOR. When PTEN was knocked down, mTOR expression increased, resulting in higher lactate production.[4] mTOR regulates PKM2, thereby affecting metabolic processes. Compared to the control group, PKM2 expression was lower in the rapamycin-treated group, while it was higher in the PTEN knockdown group. These results indicate that inhibiting mTOR also inhibits PKM2 activation, whereas excessive PKM2 expression induces mTOR activation. The purpose of simultaneously knocking down PTEN and PKM2 was to activate mTOR while inhibiting PKM2. However, there was no significant difference in glucose consumption or lactate production observed in this group. This indicates that active mTOR cannot enhance the rate of aerobic glycolysis if PKM2 is knocked down in esophageal carcinoma. The activation of mTOR regulates PKM2 to induce the Warburg Effect in cancer cells.[4] Signal transduction through mTOR also plays an important role in cancer cell proliferation. Qian reported that knocking down PKM2 suppresses glycolysis in intrahepatic cholangiocarcinoma.[26]

PKM2 INHIBITION AS CANCER THERAPY THROUGH PHYSICAL EXERCISE

The inhibition of PKM2 holds potential as a therapeutic strategy for cancer.[4] The PKM2 pathway is known to be critical in cancer cell metabolism. LY294002, a phosphatidylinositol 3-kinase (PI3K) inhibitor, has been demonstrated to suppress cancer cell proliferation. LY294002 exhibits anticancer effects in gastric cancer. It reduces the expression of p-AKT, p-mTOR, HIF-1α, and downregulates PKM2 while also inhibiting lactate dehydrogenase (LDH) activity, thereby reducing lactate production.[27] Another compound that can be used for cancer therapy by targeting PKM2 is dihydroartemisinin (DHA). DHA suppresses aerobic glycolysis in esophageal cancer by downregulating PKM2. High doses of DHA significantly decrease PKM2 expression along with the expression of several other proteins.[28]

Cancer therapy can also be supported by engaging in regular physical activity or exercise. Consistent exercise can help control the progression of cancer cells by affecting intrinsic factors such as tumor growth rate, metastasis, tumor metabolism, and immunogenicity, as well as systemic factors that regulate tumor growth, thereby reducing adverse effects.[29] The immune system plays a crucial role in managing cancer cell growth. Physical activity stimulates the mobilization of leukocytes into the

bloodstream, particularly cytotoxic T cells. Exercise can physiologically regulate cancer growth by impacting the tumor microenvironment.[30] In addition, engaging in physical activity or exercise can increase motivation to change lifestyle behaviors, improve aerobic fitness, enhance physical function, manage fatigue, and improve quality of life. Physical exercise plays a role in the treatment of various types of cancer. Lifestyle improvements can reduce cancer cell proliferation by exercising at least 3–5 hours per week. Exercise can improve healing effects related to negative reactions to cancer treatments.[31]

Physical exercise can reduce adverse effects associated with cancer treatments, enhance the curative outcomes of cancer therapies, and lower cancer risk. It inhibits cancer cell proliferation by inducing apoptosis, regulating cancer metabolism, and enhancing immune function, all of which contribute to the prevention of cancer cells. Exercise can inhibit downstream signaling pathways of PI3K and mTOR.[31] Moderate to high-intensity aerobic and resistance training has been shown to produce overall positive effects in cancer prevention and therapy. High-intensity anaerobic exercise has been shown to inhibit glycolysis even in areas distant from lactate-producing muscles, a physiological principle that can be applied as a therapeutic option to counter tumor glycolysis. Regular moderate to vigorous aerobic physical activity is beneficial in reducing the risk of various types of cancer. Exercise may contribute to tumor control, but it should be implemented cautiously and customized to the specific conditions of each individual.[32] Physical exercise also plays an important role in managing physical function, mental health, well-being, and quality of life for individuals undergoing cancer treatment and dealing with its side effects.[33]

CONCLUSION

In conclusion, pyruvate kinase M2 (PKM2) plays a pivotal role in the regulation of aerobic glycolysis in cancer cells, significantly influencing their metabolic pathways and proliferation. The article highlights that PKM2 facilitates the conversion of phosphoenolpyruvate to pyruvate, which is essential for lactate production, thereby contributing to the Warburg Effect that characterizes cancer metabolism. The interplay between mTOR signaling and PKM2 expression further underscores the complexity of metabolic regulation in cancer cells, as mTOR activation can enhance PKM2 levels, promoting glycolysis and cell growth. Importantly, the potential for targeting PKM2 as a therapeutic strategy is emphasized, with evidence suggesting that inhibiting PKM2 can disrupt glycolytic processes and reduce cancer cell viability. Overall, the findings presented in this review suggest that further exploration of PKM2 inhibitors could lead to novel cancer treatments, offering hope for improved patient outcomes in the fight against cancer.

REFERENCES

1. Courtnay R, Darleen C, Neha M, et al. Cancer metabolism and the Warburg effect: the role of HIF-1 and PI3K. Mol Biol Rep. 2015;42:841-51.

2. DeBerardinis R, Navdeep S. Fundamentals of cancer metabolism. Adv Sci. 2016;2:1-18.
3. Moench R, Grimmig T, Kannen V. Exclusive inhibition of PI3K/Akt/mTOR signaling is not sufficient to prevent PDGF-mediated effects on glycolysis and proliferation in colorectal cancer. Oncotarget. 2016;7(42):68749-67.
4. Xiaoyu H, Yin Y, Shi S, et al. The mTOR pathway regulates PKM2 to affect glycolysis in esophageal squamous cell carcinoma. Technol Cancer Res Treat. 2018;17:1-10.
5. Chen S, Cao Z, Prettner K, et al. Estimates and projections of the global economic cost of 29 cancers in 204 countries and territories from 2020 to 2050. JAMA Oncol. 2023 Apr 1;9(4):465-72. doi: 10.1001/jamaoncol.2022.7826.
6. Brown JS, Amend SR, Austin RH, et al. Updating the definition of cancer. Mol Cancer Res. 2023 Nov 1;21(11):1142-7. doi: 10.1158/1541-7786.MCR-23-0411.
7. Pavlova NN, Zhu J, Thompson CB. The hallmarks of cancer metabolism: still emerging. Cell Metab. 2022 Mar 1;34(3):355-77. doi: 10.1016/j.cmet.2022.01.007.
8. Hanahan D. Hallmarks of cancer: new dimensions. Cancer Discov. 2022 Jan;12(1):31-46. doi: 10.1158/2159-8290.CD-21-1059.
9. Igarashi Y, Sasada T. Cancer vaccines: toward the next breakthrough in cancer immunotherapy. J Immunol Res. 2020 Nov 17;2020:5825401. doi: 10.1155/2020/5825401.
10. Xie J, Wang X, Proud C. mTOR inhibitors in cancer therapy. F1000 Res. 2016;5:1-11.
11. Kennedy B, Lamming D. The mechanistic target of rapamycin: the grand conducTOR of metabolism and aging. Cell Metab. 2016;23(6):990-1003.
12. Nathan N, Keppler-Noreuil K, Biesecker L, et al. Mosaic disorders of the PI3K/PTEN/AKT/TSC/mTORC1 signaling pathway. Dermatol Clin. 2017;35(1):51-60.
13. Kim Y, Guan K. mTOR: a pharmacologic target for autophagy regulation. J Clin Invest. 2015;125(1):25-32.
14. Bostner J, Karlsson E, Pandiyan M. Activation of Akt, mTOR, and the estrogen receptor as a signature to predict tamoxifen treatment benefit. Breast Cancer Res Treat. 2013;137(2):397-406.
15. Warburg O. On respiratory impairment in cancer cells. Science. 1956;124(3215):269-70.
16. Vander HMG, Cantley LC, Thompson CB. Understanding the Warburg effect: The metabolic requirements of cell proliferation. Science. 2009;324(5930):1029-33.
17. Ward PS, Thompson CB. Metabolic reprogramming: A cancer hallmark even Warburg did not anticipate. Cancer Cell. 2012;21(3):297-308.
18. Liberti MV, Locasale JW. The Warburg effect: How does it benefit cancer cells? Trends Biochem Sci. 2016;41(3):211-8.
19. Semenza G. HIF-1: upstream and downstream of cancer metabolism. Curr Opin Genet Dev. 2010;20(1):1-10.
20. Kroemer G, Pouyssegur J. Tumor cell metabolism: Cancer's Achilles' heel. Cancer Cell. 2008;13(6):472-82.

21. Mazurek S. Pyruvate kinase type M2: a key regulator of the metabolic budget system in cancer cells. Int J Biochem Cell Biol. 2010;13:1-10.
22. Chen M, Jian Z, James L. Turning on a fuel switch of cancer: hnRNP proteins regulate alternative splicing of pyruvate kinase mRNA. Cancer Res. 2010;70:8977-80.
23. Gines A, Bystrup S, Ruiz de Porras V. PKM2 subcellular localization is involved in oxaliplatin resistance acquisition in HT29 human colorectal cancer cell lines. PLoS One. 2015;10(5):1-20.
24. Fan F, Wu H, Liu Z. Nuclear PKM2 expression, an independent risk factor for ER after curative resection of hepatocellular carcinoma. Biomed Pharmacother. 2016;84:1858-64.
25. Yuan Y, Guo-Qing P, Yan T, et al. A study of PKM2, PFK-1, and ANT1 expressions in cervical biopsy tissues in China. Med Oncol. 2012;29(4):2904-10.
26. Qian Z, Wendi H, Zhen L, et al. PKM2 upregulation promotes malignancy and indicates poor prognosis for intrahepatic cholangiocarcinoma. Clin Res Hepatol Gastroenterol. 2019;43:1291-12.
27. Lu J, Min C, Sumeng G, et al. LY294002 inhibits the Warburg effect in gastric cancer cells by downregulating pyruvate kinase M2. Oncol Lett. 2017;15:4358-64.
28. Li S, Peng H, Junqing G, et al. Dihydroartemisinin represses esophageal cancer glycolysis by downregulating pyruvate kinase M2. Eur J Pharmacol. 2019;854:232-9.
29. Hojman P, Gehl J, Christensen JF, et al. Molecular mechanisms linking exercise to cancer prevention and treatment. Cell Metab. 2018;27(1):10-21. doi: 10.1016/j.cmet.2017.09.015.
30. Zhang X, Ashcraft KA, Warner AB, et al. Can exercise-induced modulation of the tumor physiologic microenvironment improve antitumor immunity? Cancer Res. 2019;79(10):2447-56. doi: 10.1158/0008-5472.CAN-18-2468.
31. Wang Q, Zhou W. Roles and molecular mechanisms of physical exercise in cancer prevention and treatment. J Sport Health Sci. 2021;10(2):201-10. doi: 10.1016/j.jshs.2020.07.008.
32. Hofmann P. Cancer and exercise: Warburg hypothesis, tumour metabolism and high-intensity anaerobic exercise. Sports. 2018;6(1). doi: 10.3390/sports6010010.
33. Fuller JT, Hartland MC, Maloney LT, et al. Therapeutic effects of aerobic and resistance exercises for cancer survivors: A systematic review of meta-analyses of clinical trials. Br J Sports Med. 2018;52(20):1311. doi: 10.1136/bjsports-2017-098285.