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The Role of Branched-chain Amino Acids in Cancer Progression

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ABSTRACT: Despite the emergence of many therapies aimed at combating cancer, the disease provides an overwhelming global concern. Recently, the metabolism of cancer cells has been identified as an essential factor in cancer progression. The metabolism of cancer is regulated through specific dietary interventions. Further, oxidative stress plays a key role in the initiation and progression of cancer, and its impact can be influenced by tumor metabolism remodeling. Branched-chain amino acids (BCAAs), which have been shown to have functions beyond protein synthesis and energy production, are now recognized as critical regulators of oxidative stress in tumor cells. In this paper, we aim to discuss the role of BCAAs in regulating oxidative stress in tumor cells. Our study involved using prostate and renal cancer cell lines to assess the expression of anti-oxidative stress enzymes after supplementing different amino acids. Our study's results suggest that amino acids' effect on oxidative stress and signaling activation depends on the cell line and type of cancer. Our findings highlight the importance of using nutrient therapy and dietary interventions with a tailored approach and explicit reference to which kind of cancer is being treated.

KEYWORDS: Nutrition and Natural Products; Nutritional Therapy; Cancer; Oxidative Stress; Branched-Chain Amino Acids.

Introduction

1. Overview of prostate and renal cancer and epidemiology:

The epidemiology of cancer is defined by a series of multiple factors, including genetic, environmental, and lifestyle factors. According to global cancer statistics, the ailment continues to be a leading cause of morbidity and mortality worldwide, and millions of new cases continue to be diagnosed annually. Among the many types, prostate cancer and renal cancer stand out as significant contributors to the overall cancer burden.[1] Prostate cancer is the second most diagnosed cancer in men, with an increasing incidence observed with advancing age. Within prostate cancer, geographical variations exist, with higher rates reported in North America, Europe, and Australia.[2] Renal cancer, on the other hand, constitutes approximately 2-3% of all adult malignancies, with clear cell renal cell carcinoma being the most prevalent histological subtype. Its incidence varies globally, with higher rates in developed countries. This is possibly linked to lifestyle and environmental factors.[3] By understanding the distinct epidemiological patterns of prostate and renal cancers, tailored preventive and therapeutic strategies can address the unique challenges posed by these malignancies.

Nutritional therapy is pivotal in cancer's comprehensive treatment and management, improving patient outcomes and overall well-being. Cancer and its treatments often induce physiological changes that impact nutritional status, leading to malnutrition and reduced quality of life.[4] Adequate nutrition is essential for maintaining immune function, supporting tissue repair, and combating treatment-related side effects. Targeted nutritional interventions can help alleviate symptoms such as fatigue, weight loss, and compromised immune function, enhancing the patient's ability to tolerate and respond to cancer therapies. Moreover, nutrition is increasingly recognized for influencing cancer risk and progression.[5] Tailoring diets to include anti-inflammatory and antioxidant-rich foods may have a protective effect. In cancer survivors, proper nutrition aids recovery, reduces the risk of recurrence, and enhances long-term health. Collaborative efforts between oncologists, dietitians, and other healthcare professionals are essential to integrate nutritional therapy seamlessly into cancer care, emphasizing its importance as an integral component of holistic cancer management.

Branched-chain amino acids (BCAAs), comprising leucine, isoleucine, and valine, stand out among essential amino acids due to their unique structural configurations and distinct metabolic functions. Beyond serving as fundamental components for protein synthesis, BCAAs are actively involved in cellular energy metabolism and signaling pathways.[6] Notably, leucine is critical in activating the mammalian target of the rapamycin (mTOR) pathway, a central regulator of cell growth and proliferation.[7] Through mTOR, BCAAs influence protein synthesis, autophagy, and mitochondrial function, shaping the cellular response to nutrient availability and energy status. This multifaceted involvement in cellular metabolism positions BCAAs as key modulators of the intricate balance between anabolism and catabolism, making them essential players in maintaining cellular homeostasis.[8]

Understanding the interplay between BCAAs and cancer cell metabolism provides insights into potential therapeutic strategies. Targeting the unique metabolic vulnerabilities conferred by altered BCAA metabolism in cancer cells holds promise for developing novel treatment approaches, illustrating the intricate connection between nutrient availability, cellular signaling, and the complexities of cancer biology.[9]

In this study, our focus is directed explicitly towards unraveling the impact of BCAAs on the oxidative stress levels in cancer cells, recognizing the pivotal roles oxidative stress plays

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in cancer initiation and progression. The intricate interplay between oxidative stress and cancer is underscored by the opposing roles it can assume at different stages of the disease.[10] Our preliminary findings shed light on the differential effects of isoleucine, valine, and methionine in promoting the oxidative stress response within tumor cells, with varying magnitudes of influence observed across different cell lines. These nuanced results suggest that the cellular response to the same nutrients is highly contingent on the specific type of cancer and the distinct characteristics of individual cancer cell lines. Unraveling these differential responses is crucial for elucidating the complex relationship between BCAAs and oxidative stress, potentially paving the way for tailored nutritional interventions in cancer treatment based on the specific molecular and metabolic profiles of diverse cancer types.

2. Cancer Progression and Metabolic Alterations:

Cancer progression is a dynamic and intricate process characterized by a series of molecular and cellular events that collectively enable the uncontrolled growth, invasion, and metastasis of abnormal cells.[11] The hallmarks of cancer, as proposed by Hanahan and Weinberg, encompass essential traits acquired by cancer cells during this progression. These hallmarks include sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, induction of angiogenesis, and activation of invasion and metastasis pathways.[12] Importantly, accumulating evidence underscores the critical role of metabolic reprogramming as a fundamental hallmark of cancer. Cancer cells exhibit profound alterations in their energy metabolism to sustain the increased demands for cell proliferation and survival. Notably, the Warburg effect, characterized by enhanced glycolysis even in the presence of oxygen, is a well-documented metabolic adaptation in cancer cells, highlighting the shift from oxidative phosphorylation to glycolysis for energy production.[13]

The metabolic changes during cancer progression extend beyond glycolysis, encompassing alterations in amino acid metabolism, lipogenesis, and nucleotide synthesis. Cancer cells often display increased avidity for nutrients such as glucose, glutamine, and fatty acids to fuel their heightened anabolic demands.[14] Moreover, the dysregulation of key signaling pathways, including the mTOR and AMP-activated protein kinase (AMPK) pathways, contributes to the rewiring of cellular metabolism in favor of cancer cell survival and growth. These metabolic adaptations provide energy for the synthesis of macromolecules, contribute to maintaining redox balance, and support various signaling cascades implicated in cancer progression.[15,16] Oxidative stress is a well-established factor that plays a crucial role in the initiation and progression of cancer. It has a dual effect on cancer, acting as both an obstacle and a facilitator, depending on the context. On the one hand, oxidative stress poses a significant impediment to tumorigenesis, as standard cancer therapies, such as chemotherapy, exploit it to induce stress in tumor cells. On the other hand, oxidative stress also impedes tumor metastasis.[17,18] However, it should be noted that oxidative stress is intricately linked to regulating signaling pathways, which can influence tumor aggressiveness.[19] In this regard, metabolic reprogramming, particularly concerning certain nutrients, can significantly modulate oxidative stress levels, thereby exerting a profound impact on cancer progression.

2.1. Importance of metabolic reprogramming in cancer cells:

Metabolic reprogramming comes as an essential aspect of cancer progression, highlighting its significance in the formation of the malignant phenotype. Cancer cells undergo shifts in their metabolic pathways to meet the heightened demands associated with uncontrolled proliferation, survival, and metastasis. The Warburg effect, a hallmark metabolic shift towards increased glycolysis, exemplifies this reprogramming. This highlights the preference of cancer cells for anaerobic energy production, even in oxygen-rich environments. Beyond glycolysis, cancer cells manipulate other metabolic pathways, including amino acid metabolism, lipid synthesis, and nucleotide production, to sustain their accelerated growth and division.[20]

The importance of metabolic reprogramming in cancer extends beyond merely providing energy and building blocks for cellular components. It plays a crucial role in supporting the redox balance and cellular signaling pathways essential for cancer cell survival. Dysregulated nutrient sensing through key signaling hubs such as mTOR and AMPK contributes to the altered metabolic landscape observed in cancer cells, ensuring a continuous supply of nutrients to sustain their aggressive phenotype.[21] Recognizing the centrality of metabolic reprogramming offers promising avenues for therapeutic interventions. Targeting the vulnerabilities inherent to cancer cell metabolism provides a foundation for developing precision medicine approaches that exploit these unique metabolic dependencies, offering potential breakthroughs in cancer treatment and management.[22]

2.2. Role of amino acids in cancer metabolism:

Amino acids play critical roles in cancer metabolism, contributing significantly to the progression and sustenance of malignant tumor cells. Beyond their traditional role as building blocks for protein synthesis, amino acids are essential to many aspects of cancer metabolism. First, amino acids are necessary for energy production and cellular respiration, as they are crucial substrates for these cellular processes. Secondly, amino acids regulate signaling pathways that orchestrate cell growth, survival, and proliferation. For example, the mTOR pathway, which integrates nutrient sensing and growth factor signaling, is regulated by the expression of amino acids, especially leucine. Activating the mTOR signaling pathway promotes protein synthesis, cellular growth, and metabolism. These key factors make amino acids key moderators of cancer cell anabolism. Moreover, amino acids contribute to the maintenance of redox balance within cancer cells. Amino acids have been found to influence cellular responses to oxidative stress and support cell survival. Further recognizing the pivotal role of amino acids in cancer metabolism may offer a potential pathway for using BCAAs for therapeutic intervention. Targeted strategies aiming to utilize the effect of amino acids on cancer's metabolic dependencies suggest the development of a more effective and tailored approach to treating cancer.[23]

3. Branched-chain amino Acids (BCAAs) and cancer progression:

Branched-chain amino acids (BCAAs), encompassing leucine, isoleucine, and valine, wield significant influence over cancer cell biology due to their diverse roles in cellular metabolism and signaling. The dysregulated metabolism of BCAAs in cancer cells can markedly impact critical processes associated with oncogenesis. Moreover, BCAAs contribute to the metabolic reprogramming observed in cancer, influencing energy pathways and supporting the increased anabolic demands required for accelerated growth. Additionally, BCAAs are crucial in maintaining redox balance within cells, affecting the cellular response to oxidative stress—a factor with dual implications in cancer progression.[24,25]

Recognizing the multifaceted impact of BCAAs in cancer biology offers a foundation for exploring novel therapeutic avenues. The intricate involvement of these amino acids in key cellular processes positions them as potential targets for therapeutic interventions. By modulating BCAA metabolism or targeting specific pathways activated by these amino acids, innovative strategies for cancer treatment are likely to be developed. Continued research in this area holds promise for uncovering the precise mechanisms underlying the influence of BCAAs on cancer progression, paving the way for tailored therapeutic approaches that exploit the metabolic vulnerabilities inherent to cancer cells.

Methods

4.1. Methods:

4.1.1. Cell culture and cell treatment:

This study utilized human prostate cancer cell lines, 22Rv1 and PC3, and renal cancer cell lines, SKRC7 and SKRC11. These tumor cells were sourced from the American Type Culture Collection (ATCC) sustained in RPMI1640 medium and enriched with 10% fetal bovine serum (FBS) and 1% Penicillin-Streptomycin antibiotics. The cells underwent cultivation in a controlled environment with 5% CO_2 at 37 degrees Celsius to ensure optimal conditions for growth and maintenance. To investigate the specific impact of different types of amino acids on these cancer cells, the cells were cultured in RPMI supplemented with 10% dialyzed FBS, in which small molecules, including fatty acids, were removed from the serum. Subsequently, the cells were treated with 1 mM concentrations of amino acids, which is a standard dosage commonly used for this type of treatment. This treatment protocol was maintained for different periods.

4.1.2. Western blotting:

The Western blot analysis involved a systematic procedure for the treated cells. Initially, the cells were washed in ice-cold PBS and lysed in RIPA buffer containing protease and phosphatase inhibitors. The resulting cell lysates underwent centrifugation, and total protein concentrations were determined using the BCA Protein Assay Kit to ensure equal loading onto SDS-PAGE gels for electrophoresis. The separated proteins were then transferred to PVDF membranes, which were subsequently blocked with 5% non-fat milk in TBST. Following blocking, the membranes were probed overnight at 4°C with specific primary antibodies. The primary antibodies were diluted using Intercept (PBS) Blocking Buffers (LICORBio, 927-70001). The primary antibodies target the following proteins: p-S6k (Cell Signaling Technology, #9234, 1:2000), S6K (Cell Signaling Technology, #34475, 1:1000), p-S6 (Cell Signaling Technology, #5364, 1:2000), S6 (Cell Signaling Technology, #2317, 1:1000), GPX1 (Cell Signaling Technology, #3206, 1:1000), SOD2 (Cell Signaling Technology, #13141, 1:1000), Catalase (Cell Signaling Technology, #14097, 1:1000), and Vinculin (Cell Signaling Technology, #13901, 1:2000). After washing, the membranes were exposed to suitable horseradish peroxidase-conjugated secondary antibodies, and densitometric quantification was done by visualizing and quantifying protein bands using the LI-COR Odyssey CLx Imaging System. The bind intensity was normalized to the control group on each membrane and the normalized quantification was shown under each blot. This comprehensive Western blotting approach provided valuable insights into the molecular alterations induced by the treatment, elucidating the activation status of crucial signaling pathways and protein expression levels. It would have been beneficial for the analysis if an oxidative stress assay was performed. However, time constraints and resource availability prevented such.

Result and Discussion

5. Results:

5.1. The effects of amino acids on mTOR signaling:

The mTOR signaling pathway is recognized as a pivotal player in cancer, influencing cellular processes such as proliferation, survival, and metabolism.[26] In our study, the impact of branched-chain amino acid (BCAA) supplementation on mTOR signaling activity in prostate and renal cancer cells showed various results. Following a six-hour BCAA supplementation, the phosphorylation levels of S6K and S6, indicative of mTOR pathway activation, were measured. For prostate cancer cells, the 22Rv1 cell line exhibited enhanced activation of S6K and S6 in response to leucine, valine, and methionine, while no discernible effect was observed in the PC3 cell line.

In Figure 1, in renal cancer cells, a divergent pattern was noted. In the SKRC11 cell line, all amino acids, with valine having a particularly pronounced effect, promoted S6K phosphorylation. However, no significant difference was observed in the SKRC7 cell line. Interestingly, isoleucine and valine demonstrated the ability to induce S6 phosphorylation in renal cancer cells. However, the effect was absent in the SKRC7 cell line. These findings underscore the nuanced and context-dependent nature of the response to amino acid supplementation within cancer cells, even when considering cells of the same cancer type. The intricate interplay between specific amino acids and mTOR signaling activation appears to be intricately linked to the specific genetic and molecular characteristics of individual cancer cell lines, emphasizing the importance of considering cellular heterogeneity in designing targeted therapeutic approaches.

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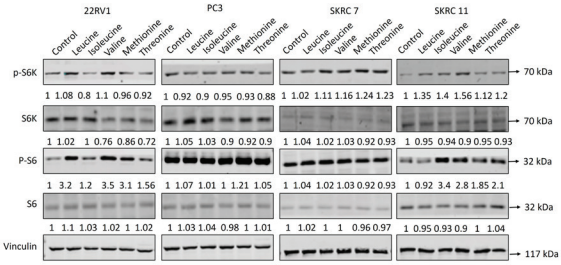

Figure 1: The effect of BCAAs on mTOR signaling activity. The tumor cells were treated with 1mM of different amino acids for 6 hours, and then the phosphorylation levels of S6K and S6 were measured to indicate the mTOR signaling activity. The interplay between the following amino acids and mTOR signaling activation depends on the characteristics of the individual cancer cell line. The western blots were repeated 3 times.

5.2. The effect of amino acids on oxidative stress:

Oxidative stress is a critical obstacle to cancer progression. Therefore, the anti-oxidative stress ability of tumor cells is critical for its survivability and proliferation.[27] Multiple enzymes play an essential role in oxidative stress. Glutathione peroxidase 1 (GPX1) is an abundant and widely expressed antioxidant enzyme that reduces oxidative stress by fighting the formation of damaged free radicals in the reproductive system. GPX1 is often associated with certain types of cancer in which the enzyme is abnormally elevated. However, GPX1 has complex opposite roles in tumor-suppressing and promotion in different cancers.[28] In some cancers, GPX1 is known to take place in various signaling pathways to regulate tumor behavior such as cell proliferation, oxidative stress, immune response, metastasis, and chemoresistance. Further, high levels of GPX1 in RCC patients have been associated with distant lymphatic metastasis and tumor stage. Elevated levels of GPX1 can also be used as a distinguishing factor between RCC and normal subjects.[29] On the other hand, GPX1 does not have a significant association with prostate cancer.[30] Catalase is one of the most important enzymes in regulating oxidative stress and speeds the decomposition of hydrogen peroxide as its substrate. Like GPX1, catalase plays a dichotomous role in cancer regulation, acting as a tumor suppressor and a prosurvival protein during tumor progression.[31] In renal cell carcinoma, tumor tissue has been found to have lower enzyme levels compared to normal tissue. In prostate cancer, catalase could be a potential target to slow down tumor growth. Superoxide dismutases (SOD2) are a group of metalloenzymes constituting a strong antioxidant defense against oxidative stress.[32] SOD2 has a dichotomous role in cancer metabolism as it may act as a tumor suppressor and progressor. For its tumor suppressive function, SOD2 drives tumorigenesis and proliferation. On the other hand, the activation of SOD2 may result in enhanced O_2- O_2-scavenging, which results in the role of SOD2 in tumor progression. The expression of these proteins indicates the ability of oxidative stress. An increased amount of expression in GPX1, catalase, and SOD2 suggests that there is an increased level of oxidative stress as a response to the imbalance of prooxidants and antioxidants.[33]

5.2.1 .The effect of short-term treatment of amino acids:

Despite considering that the cells are the same type of cancer, the one-hour treatment of the following two lines of prostate cancer, 22Rv1 and PC3, displayed noticeable variations in the concentrations of enzymes between them. Firstly, it is important to note that there is no significant difference in vinculin throughout the numerous variables. Vinculin acts as a loading control for the accuracy of the western blot, and its consistency suggests that the following enzymes are accurately expressed. From these results, the expression of the enzyme is dependent on the cell line.

As seen in Figure 2, in 22Rv1, the concentration of GPX1 is consistent with the control among leucine, isoleucine, and valine. However, the concentration of GPX1 decreases in 22Rv1 under valine and threonine. Interestingly, the PC3 cell line of prostate cancer shared different results in the GPX1 enzyme, with the concentration of all six variables consistent throughout. The expression of the GPX1 enzyme also varies in the two cell lines of renal cancer. SKRC7 has significantly more GPX1 expressed under conditions of isoleucine and valine, and SKRC11 has significantly more GPX1 expressed under methionine but slightly more under isoleucine and valine. The GPX1 enzyme also seemed less expressed under threonine for cell line SKRC7.

In Figure 2, the enzyme catalase also differed between cell lines of the same cancer. In 22Rv1, the concentration of catalase was higher in methionine. PC3, on the other hand, had higher levels of catalase expressed in isoleucine and valine. The rest of the variables were consistent with the control. However, the catalase expression in renal cell cancer lines was similar throughout SKRC7. In cell line SKRC11, threonine catalase levels were slightly higher, while the condition under valine was slightly lower.

Finally, also in Figure 2, the protein SOD2 ranged between cell lines of the same cancer. In 22Rv1, the expression of SOD2 was similar among all the BCAA except for methionine, which was slightly lighter, suggesting that lower levels of SOD2 were expressed under catalase. The case was different for PC3 despite the cell line being the same type of cancer, with expression levels of SOD2 having no significant difference throughout. In renal cancer cell lines, the SOD2 expression levels are slightly darker under conditions of valine and methionine, suggesting an increase. While another cell line of renal cancer, SKRC11, showed lower levels of SOD2 expression in samples of methionine and threonine.

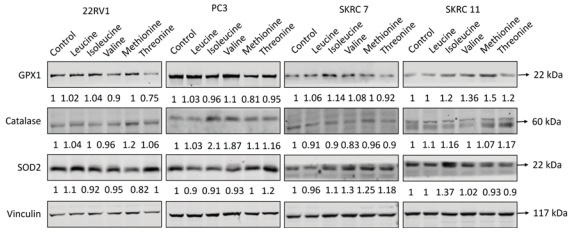

Figure 2: The impact of BCAAs on the expression of antioxidant enzymes. Tumor cells were treated (as a short-term treatment) with 1 mM concentrations of various amino acids over one day. Subsequently, the protein levels of several antioxidative stress enzymes were assessed to evaluate the cells' antioxidant capabilities. The role of BCAAs in the expression of antioxidant enzymes in a short-term treatment seems to revolve around the specific characteristics of the cancer cell line. The western blots were repeated 3 times.

5.2.2. The effect of long-term treatment of amino acids:

Figure 3 demonstrated the long-term treatment GPX1 expression showed no significant difference between leucine, valine, and threonine in 22Rv1. However, conditions under isoleucine and leucine had significantly less expression in the enzyme. In cell line PC3, there is no significant difference. Interestingly, in this spectrum of renal cancer, the SKRC7 cell line showed significantly more expression in GPX1 under valine, methionine, and threonine conditions. In contrast, another cell line, SKRC11, only showed more expression in valine and methionine.

The long-term expression of catalase shown in Figure 3 varied between cell lines despite being the same type of cancer. For 22Rv1, there were decreased levels of catalase in the cells under the condition of leucine and methionine. PC3, however, has no significant differences in the expression of the enzyme. In the renal cancer cell lines, there is an increase in the expression of catalase in cell line SKRC7 when introduced with isoleucine, valine, methionine, and threonine, and a small decrease in the expression of catalase in SKRC11 under methionine and threonine.

Figure 3's SOD2 has also shown differences in expression between cell lines, although it is part of the same cancer family. In 22Rv1, there is a slight increase in SOD2 in the isoleucine treatment and a decrease in SOD2 in methionine and threonine. Nevertheless, PC3 significantly increases SOD2 under isoleucine, valine, and methionine. SOD2 expression variation held the same principle in renal cancer. SKRC7 showed no difference in expression between the amino acids. However, SKRC11 showed an increase in the expression of SOD2 in valine, with the other variables showing very little expression in SOD2.

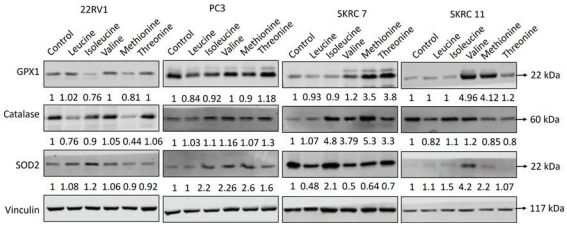

Figure 3: The impact of long-term treatment of BCAAs on the expression of antioxidant enzymes. Tumor cells underwent a prolonged treatment regimen with 1 mM concentrations of diverse amino acids for five days. Following this period, the protein levels of multiple antioxidative stress enzymes were analyzed to gauge the cells' antioxidant capacities. The role of BCAAs in the expression of antioxidant enzymes in a long-term treatment seems to revolve around the specific characteristics of the cancer cell line. The western blots were repeated 3 times.

5.3. Densitometric quantification of ROS levels of amino acid treatments:

Figure 4's relative DCF fluorescence in renal cancer cell line SKRC11 under the conditions of 1mM amino acid treatment displays a significant difference in comparison to the control in BCAAs isoleucine and valine. Specifically, the tumor cells under 1mM isoleucine and valine have approximately 20-30% more DCF fluorescence compared to the control. This suggests that isoleucine and valine promote higher ROS levels which may in turn induce cell proliferation. Interestingly, this data is consistent within the morphology of the 3d spheroid cultures. The spheroids of the isoleucine and valine culture exhibit an increased size, correlating with higher ROS level which enhances cell proliferation.

The relative DCF fluorescence (Figure 4) in prostate cancer cell line DU145 shared similarities with renal cancer cell line SKRC11. The tumor cells reacted mostly to isoleucine and valine, which caused an approximately 10% increase in DCF fluorescence compared to the control. Like the cancer cell line SKRC11, the 3D spheroid culture under isoleucine and valine supplementation demonstrates a larger morphology, indicating increased cell proliferation. Isoleucine and valine may play a similar role within the mTOR signaling pathway as these two amino acids are seen to increase ROS level and cell proliferation.

In Figure 4 interestingly, isoleucine and valine only slightly elevate the ROS levels in tumor cells. However, these two amino acids drastically increase ROS levels in non-tumor HEK293 cells. The levels of DCF fluorescence are approximately 30-40% higher compared to the control. Additionally, the DCF level under histidine supplementation decreases approximately 20%, suggesting that histidine may inhibit cell proliferation as it lowers ROS levels.

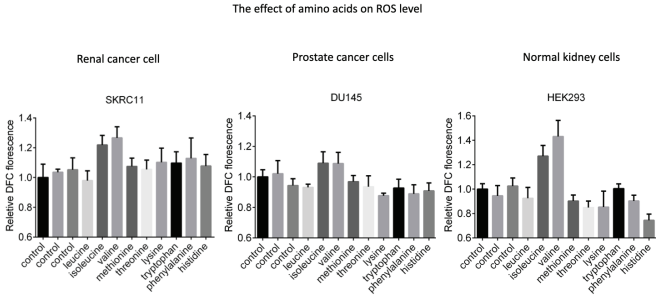

Figure 4: The impact of BCAAs on the ROS levels. Tumor cells were treated with 1 mM concentrations of various amino acids. Subsequently, the ROS levels of several amino acid conditions were assessed to evaluate the cells' antioxidant capabilities.

6. Discussion:

In this study, tumor cells reacted differently to amino acids based on the type of cancer cells. No single expression of the protein is the same between cell lines. The protein expression will describe a cell's ability to tolerate stress, suggesting that throughout the treatments of BCAA, there is a high variation between cell lines despite being in the same cancer family. Further, other key implications of BCAA in cancer proliferation are raised. The cell's ability to tolerate stress displays the cell's survival rate. If the cancer cell has a strong ability to tolerate stress, then the survival rate of the cell is higher, and vice versa. The antioxidants GPX1, catalase, and SOD2 all play an essential role in cancer cells' oxidative stress levels. As antioxidants scavenge free radicals to balance stress levels in cells, the change in regulation of these antioxidants leads to oxidative stress.

The implications of BCAA as a potential therapy for cancer range based on the type of cancer and the cell line. From this study, it can be inferred that the same amino acids have different effects on different cancer cell lines despite the tumor

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being the same type. Henceforth, the specificity of the cell line plays a significant role in cancer progression in BCAA metabolism. This may propose that BCAA be used as a variation in cancer treatment. For instance, the amino acid leucine methionine decreases the amount of catalase expression in 22Rv1 in long-term treatment. Therefore, 22Rv1 cells under these conditions have a lower survival rate. BCAA therapy may be used as treatment through a tailored approach to target tumor cells based on the specific characteristics of their reaction to amino acids. However, this has many limitations, as BCAA therapy is based on a particular cell line.

BCAA in cancer therapy may not be universal for every type of cancer. In Figures 1, 2, and 3, the expression of the proteins may be lower or higher under the same treatment as a different cell line from the same cancer. Therefore, the implementation of BCAA as a therapeutic target in cancer treatment comes with many challenges. From this study, it can be inferred that the effect of BCAA on cancer varies by cell line. No specific treatment exists for the onslaught of numerous cell lines. Furthermore, BCAA therapy may face a temporal issue. The response of the cells may differ and change over time in response to the BCAA, thus making this type of treatment unpredictable and complex. Although there is a lack of universal therapy, BCAA therapy may be used in the future for diverse cancer types by offering a nuanced approach. While the challenges are evident, hope for BCAA therapy as a potential component in a multifaceted treatment plan is present.

■ Conclusion

BCAA-based therapy may be further researched on other cancer cell lines to explore their mechanisms in targeting specific metabolic pathways. Investigating the molecular mechanisms due to BCAA within cancer cells may reveal key pathways in mediating the anti-cancer effects. Despite the challenges of protein expression variation in different cell lines, optimizing potential strategies for BCAA-based therapy is promising. BCAA-based therapy may be refined in the future for patients to have dietary interventions to treat cancer. BCAA-based therapy may also be successful in working along with other types of cancer treatment. The fluctuation of protein expression and its ability to tolerate stress correlates with the survival rate in a cell population. A combination therapy between BCAA and other treatments may be successful if the proper BCAA treatment is applied to weaken the cells for another stronger treatment.

The future approach in this study is to investigate cancer cells' survival rates based on their ROS and oxidative stress levels. ROS manipulation is a potential target for cancer therapies, and BCAA therapy will be further explored to see its implications on ROS levels. High ROS levels have been associated with increased apoptosis, while oxidative stress plays a dichotomous role in cancer progression. Low oxidative stress has been used as a treatment strategy for preventing tumorigenesis in non-cancer patients, and highly elevated levels of oxidative stress are used to kill tumor cells in other cancer therapies. Based on this, we will further investigate the effects of BCAA on cancer metabolism through the cell's survival rate in various levels of oxidative stress. This area of exploration will reveal more about the cell's metabolic pathway in reaction to conditions under BCAA and give quantified data on the specific cell line's survival rate based on ROS level and oxidative stress.

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