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SHORT COMMUNICATION

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Role of Glutaminase-Antioxidant Axis in Cancer and Metabolic Disorders

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Description

Glutaminase is an enzyme that plays a critical role in cellular metabolism, particularly in the catabolism of glutamine, an essential amino acid. It catalyzes the hydrolysis of glutamine to glutamate, which can then be converted into α-ketoglutarate, a key intermediate in the Tricarboxylic Acid (TCA) cycle. This metabolic pathway is important for maintaining cellular energy production, especially in cells with high proliferative demands, such as cancer cells. Glutamine is a versatile amino acid that contributes to multiple metabolic pathways, including energy production, biosynthesis of nucleotides, and maintenance of redox homeostasis. Glutaminase (GLS) catalyzes the conversion of glutamine to glutamate, which can enter the TCA cycle and generate ATP. This metabolic process is particularly important in cells that undergo rapid proliferation, such as immune cells during inflammation and cancer cells.

Oxidative stress and glutaminase

Oxidative stress arises when there is an imbalance between the production of Reactive Oxygen Species (ROS) and the ability of the body's antioxidant defenses to neutralize them. ROS, such as hydrogen peroxide (H_2O_2) and superoxide anions, are by products of cellular metabolism, particularly in mitochondria. At physiological levels, ROS act as signaling molecules. However, excessive ROS production can damage cellular components, including lipids, proteins, and DNA, leading to oxidative stress and contributing to the pathogenesis of various diseases, including cancer, cardiovascular disorders, and neurodegeneration [1].

The connection between glutaminase and oxidative stress is twofold. First, glutaminase activity influences the availability of glutamate, a precursor for the synthesis of Glutathione (GSH), the body's most abundant intracellular antioxidant [2]. GSH plays a vital role in neutralizing ROS and maintaining redox homeostasis. Elevated glutaminase activity can enhance the supply of glutamate, facilitating GSH synthesis and bolstering antioxidant defenses [3].

Antioxidants: Mechanisms and benefits

Antioxidants are molecules that neutralize ROS and mitigate oxidative damage. They can be classified into enzymatic and non-enzymatic antioxidants [4]. The antioxidant properties of glutaminase and its metabolites offer several potential benefits, particularly in the context of various diseases.

Cancer: Cancer cells often exhibit altered metabolism, with increased reliance on glutamine for growth and survival. By modulating glutaminase activity, it may be possible to enhance oxidative stress within tumor cells, thereby promoting cell death while sparing normal cells. Research is ongoing to analyse the therapeutic potential of glutaminase inhibitors in cancer treatment [5].

Neurodegenerative diseases: Glutamate is essential for brain health, but excessive levels can lead to excitotoxicity, contributing to neurodegenerative conditions such as Alzheimer's and Parkinson's diseases [6]. Maintaining optimal glutamate levels through glutaminase activity may help protect neurons from oxidative damage and promote cognitive function [7].

Inflammatory disorders: Conditions characterized by chronic inflammation, such as rheumatoid arthritis and inflammatory bowel disease, can benefit from enhanced antioxidant defenses [8]. By boosting GSH levels through glutaminase activity, it may be possible to reduce oxidative stress and inflammation, leading to improved clinical outcomes [9].

The interplay between glutaminase, oxidative stress, and antioxidants is especially important in cancer cells. On the one hand, elevated glutaminase activity supports

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cancer cell proliferation and survival. On the other hand, the resulting oxidative stress can be detrimental to these cells. Antioxidants, while generally beneficial in normal cells, may have a dual role in cancer. By neutralizing ROS, antioxidants can potentially protect cancer cells from oxidative damage, inadvertently promoting their survival. In metabolic disorders such as obesity and diabetes, oxidative stress is a well-documented contributing factor to disease progression [10]. Glutaminase-driven GSH production can help mitigate oxidative stress in these conditions, and antioxidants can further bolster this protective mechanism. For example, dietary antioxidants such as polyphenols and vitamins C and E have shown promise in reducing oxidative damage and improving metabolic outcomes in these diseases.

Glutaminase plays a pivotal role in cellular metabolism, contributing to energy production, biosynthesis, and redox balance. However, its activity is also associated with increased oxidative stress, particularly in highly proliferative cells like cancer cells. Antioxidants, both endogenous and exogenous, provide a protective mechanism by neutralizing ROS and maintaining cellular homeostasis.

References

[1] Matés JM, Campos-Sandoval JA, de Los Santos-Jiménez J, Márquez J. Dysregulation of glutaminase and glutamine synthetase in cancer. Cancer Lett 2019; 467:29-39.

[2] Chen L, Cui H. Targeting glutamine induces apoptosis: A cancer therapy approach. Int J Mol Sci 2015;16(9):22830-22855.

[3] Melis GC, ter Wengel N, Boelens PG, van Leeuwen PA. Glutamine: Recent developments in research on the clinical significance of glutamine. Curr Opin Clin Nutr Metab Care 2004;7(1):59-70.

[4] Simon J, Nuņez-García M, Fernández-Tussy P, Barbier-Torres L, Fernández-Ramos D, Gómez-Santos B, Buqué X, et al. Targeting hepatic glutaminase 1 ameliorates non-alcoholic steatohepatitis by restoring very-low-density lipoprotein triglyceride assembly. Cell metab 2020;31(3):605-622.

[5] Aron-Wisnewsky J, Vigliotti C, Witjes J, Le P, Holleboom AG, Verheij J, et al. Gut microbiota and human NAFLD: Disentangling microbial signatures from metabolic disorders. Nat Rev Gastroenterol Hepatol 2020;17(5):279-297.

[6] Canbay A, Götze O, Kucukoglu O, Weinert S, Croner RS, Baars T, et al. L-Ornithine-l-Aspartate (LOLA) normalizes metabolic parameters in models of steatosis, insulin resistance and metabolic syndrome. Pharmaceutics 2024;16(4):506.

[7] Cyriac R, Lee K. Glutaminase inhibition as potential cancer therapeutics: Current status and future applications. Journal of Enzyme Inhibition and Medicinal Chemistry 2024 ;39(1):2290911.

[8] Oliveira AK, de Oliveira e Silva AM, Pereira RO, Santos AS, Barbosa Junior EV, Bezerra MT, et al. Anti-obesity properties and mechanism of action of flavonoids: A review. Crit Rev Food Sci Nutr 2022;62(28):7827-7848.

[9] Adamoski D, M. dos Reis L, Mafra AC, Corrêa-da-Silva F, Moraes-Vieira PM, Berindan-Neagoe I, et al. HuR controls glutaminase RNA metabolism. Nat Commun 2024;15(1):5620.

[10] Kim HJ, Seo JY, Suh HJ, Lim SS, Kim JS. Antioxidant activities of licorice-derived prenylflavonoids. Nutr Res Pract 2012;6(6):491.