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Commentary

AMMONIUM TOXICITY IN CANCER CELLS

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DESCRIPTION

Ammonia is a widespread by-product of cellular metabolism, but its biological ramifications, particularly in cancer, are not well known. Ammonia was largely assimilated by cancer cells via reductive amination catalysed by glutamate dehydrogenase (GDH), with additional processes allowing other amino acids, such as proline and aspartate, to obtain nitrogen directly. Breast cancer proliferation was increased by metabolic recycling of ammonia. Increased food consumption can meet the vast bioenergetic, biosynthetic, and pro-survival needs of rapidly reproducing cells by supplying carbon, nitrogen, oxygen, and sulphur. As a result, such cells produce an overabundance of metabolic waste, which is eliminated by animals' excretory system. However, metabolic byproducts such as lactate and ammonia build in the tumour microenvironment. Although lactate is well studied in cancer, little is known about how cancer cells deal with elevated levels of ammonia (NH3) produced by glutamine and asparagine catabolism, de novo cysteine synthesis via the transsulfuration route, and salvage nucleotide metabolism.

Ammonia has long been thought to be a hazardous by-product that must be evacuated from cells and then removed in the liver via the urea cycle. Because of its anabolic role in nucleotide synthesis, glutamine has been dubbed a "nitrogen reserve" for cancer cells. However, in catabolic glutamine metabolism, nitrogen is freed as the by-product ammonia, contradicting glutamine's

role as a nitrogen store. Ammonia's fate in the metabolism of proliferating cells and tumors is unknown.

Carbamyl phosphate synthetase I (CPS1), the ATP-dependent, rate-limiting step of the urea cycle; glutamate dehydrogenase (GDH), a NAD(P)H-dependent enzyme that catalyzes reductive amination of -ketoglutarate; and glutamine synthetase (GS), which catalyzes the ATP-dependent amination of glutamate to generate glut The Cancer Genome Atlas transcriptome data for ammonia-assimilating enzymes in healthy and malignant tissues found that GS and GDH mRNA expression was considerably raised across multiple cancer subtypes, although CPS1 expression was only enhanced in colon. GS and GDH are widely expressed in healthy tissues, whereas CPS1 is only found in the liver. Both GS and GDH were shown to be overexpressed in breast tumors.

Specifically, GS and GDH expression is higher in ER-positive breast tumors than in other subtypes. We looked at whether free ammonia may be assimilated into metabolic pathways because several processes generate ammonia in addition to glutaminolysis. Ammonia at supraphysiological concentrations is harmful to neurons and is sometimes considered to be hazardous to tumor cells as well. However, even at concentrations that were hazardous to native human astrocytes, NH4Cl was not harmful to tumor cells. High amounts of ammonia have been demonstrated to trigger autophagy in tumor cells in previous studies.

Metabolic reprogramming is a well-known cancer symptom. Metabolic proteins and/or metabolites can affect gene and protein expression, making them possible diagnostic and prognostic biomarkers. Certain metabolites, such as lactate and amino acid, have yielded reliable results, and their changes in serum reflect metabolic changes in tumor tissue. Many studies have been conducted to find serum biomarkers for HCC diagnosis that are related to metabolism. Cancer cells rely on glutamine for survival and growth in addition to glucose. Glutamine catabolism is accompanied by alanine and ammonia secretion, resulting in the loss of most glutamine amino groups from the cell rather than their incorporation into other molecules. They contribute to the buildup of ammonia in the tumor microenvironment when combined with other amino acid metabolism.

Ammonia metabolism appears to play a variety of roles in cancer. The liver is an ideal metabolic model that regulates body energy metabolism by physiologically regulating various metabolites such as sugars, lipids, amino acids, and the urea cycle. Normal liver cells produced less ammonia but expelled more urea than cancer cells, according to cell tests. The expression of CPS1 may have a minor impact on urea metabolism in cancer cells.

Furthermore, the urea cycle may help cancer cells proliferate by detoxifying excessive levels of ammonia. It is still difficult to find accurate non-invasive biomarkers that may be utilized broadly. Many plasma/serum metabolic indicators for the early diagnosis of HCC have been reported to date. However, because most clinical laboratories are unable to detect biomarkers, only a handful have been employed in the clinical diagnosis of HCC. HCC patients had considerably greater serum urea than healthy controls and patients with other liver disorders. Furthermore, patients with lung cancer, breast cancer, and colorectal cancer had considerably greater serum urea.

CONFLICT OF INTEREST

None.

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