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Reliance of tumor growth and associated angiogenesis on glutamine-an overview

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ABSTRACT

Tumor-bearing state is accompanied by changes in host as well as cancer cell metabolism of several amino acids. Among these amino acids, glutamine holds a special position in tumor cell metabolism as it is an abundant and versatile nutrient that takes part in multiple cellular processes. It not only participates in energy production, but also contributes to redox homeostasis, signaling and macromolecular synthesis within cancer cells. Being an important component of the extracellular matrix protein, fibrin, glutamine is also known to contribute to tumor-induced angiogenesis. The diverse regulatory roles played by this amino-acid makes it a desirable therapeutic target in cancer. The present study throws light on the various aspects of glutamine metabolism in cancer cells and the future prospects of diagnostic and therapeutic strategies that can be deployed in this arena.

Keywords- glutamine, tumor, angiogenesis

INTRODUCTION

Metabolic alterations are recognized as one of the 10 hallmarks of cancer (Hanahen and Weinberg, 2011) that distinguish transformed cells from their healthy counterparts. Changes in metabolism not only facilitate rapid proliferation of the cancer cells but also help them to survive hypoxia and promote neovascularization. Currently the study of small molecule metabolites, also known as metabolomics, has emerged as an important tool in the diagnosis of different types of cancer (Kaushik and DeBerardinis, 2018; Chen *et al*., 2011; Rocha *et al*., 2011; Louis *et al*., 2016).

The uncontrolled proliferation of neoplastic cells is accompanied by metabolic alterations which lead to increases in nucleotide and protein synthesis. A continuous supply of both essential and non-essential amino acids is necessary for the high rate of protein synthesis by malignant cells (Medina *et al*., 1988). Rapidly proliferating

cells also require a huge supply of energy substrates. Glutamine efficiently serves both the purposes (Newsholm and Parry-Billings, 1990) and therefore many authors believe that tumors behave as "glutamine traps" (Klimberg and McClellan, 1996; Souba 1993). The diverse functions of glutamine in various crucial metabolic pathways of cancer cells well justifies its role as a super nutrient in supporting malignancy.

Background- Prof. Hans Kreb first recognized the importance of glutamine for cell function (Brosnan 2001). Skeletal muscle is the major site of glutamine synthesis within the body (Welbourne 1987) from where it is released into the bloodstream and transported to a variety of tissues (Young and Ajami, 2001). The presence of a tumor produces such great changes in host glutamine metabolism that host nitrogen metabolism is accommodated to the tumor-enhanced requirements of glutamine (Medina 2001). During stress and hypercatabolic states such as cancer, a new steady state is reached with a lower intracellular glutamine concentration and an elevated rate of glutamine release maintained by its increased synthesis (Lacey and Wilmore, 1990). Glutamine must be transported into tumor mitochondria to be used (Medina 2001). Roberts *et al* showed that tumor regression is accompanied by an increase in the concentration of free glutamine in C1498 leukemia (Roberts 1955). Furthermore, there is no detectable amount of free glutamine in the rapidly developing leukemia. Tumors are avid glutamine consumers. High rate of glutaminolysis is necessary in cancer cells to allow sensitive and precise control of the pathways which generate metabolic intermediates for macromolecular biosynthesis.

Glutamine and tumor growth-

The mediator of uptake of circulating glutamine by the cancer cells is alanine-serine-cysteine-transporter-2 (Wise and Thompson, 2010). This receptor is found to be overexpressed in squamous cell carcinoma, adenocarcinoma and neuroendocrine lung tumors (Hassanein *et al*., 2019). The importance of glutamine for the malignant cells can be explained by the following facts:

- Glutamine is the most abundant and versatile of all amino acids in the body (Bergstrom *et al*., 1974; Smith 1990). Evidences indicate that glutamine is the major respiratory fuel for tumor cells (Reitzer *et al*., 1979; Kovacevic and Marris, 1972). Glutamine has been shown to be an unusually good substrate for oxidation by tumor cell mitochondria where it is acted upon by glutaminase.
- The demand for glutamine is higher compared to other amino acids in certain neoplasms (Petit 1977). Fast-growing fibrosarcomas are excellent glutamine consumers (Fischer and Chance,1990).
- Malignant cells transport glutamine across their plasma membrane at a faster rate than their non-malignant counterparts (Souba 1993), by means of Na+-dependent amino acid-transport systems (Medina *et al*., 1991), and across the inner mitochondrial membrane by a carrier-mediated system (Molina *et al*., 1995). Malignant cells have a high oxidative glutamine metabolism and that there is direct correlation between such oxidation and the degree of malignancy.
- Compared to normal body cells, tumor cells typically operate at limiting levels of glutamine availability. This is due to increased utilization and reduced production of glutamine (Weber 1983).
- Many enzymes utilize glutamine for specific reactions, most notably the family of eight amidotransferases involved in the synthesis of purines, pyrimidines, glucosamines, NAD+ and asparagine. The formation of glutamine phosphorybosylpyro phosphate by amido phosphorybosyl transferase from ribose-5-phosphate is the first step of the de novo synthesis of purines. In case of pyrimidines, de novo synthesis begins with the formation of carbamyl phosphate from glutamine, carbon dioxide and adenosine triphosphate (Engstrom 1984).
- L-glutamic acid and L-glutamine are interconvertible by usual biotransformation process and glutamic acid occurs in many different types of malignant tumors.
- Glutamine serves as an important source of carbon and is primarily utilized for TCA cycle anaplerosis.
- Glutamine is the most important circulating "nitrogen shuttle" accounting for 30% to 35% of all amino acid nitrogen transported in the blood (Souba 1987).
- Glutamine functions as the main vehicle for circulation of ammonia in a non-toxic form (Medina 1992) from peripheral tissues to visceral organs where the ammonia can be excreted as ammonium (kidneys) or converted to urea (liver).
- Findings suggest that the activities of glutamine-using enzymes such as glutaminase or CTP synthetase, carbamoyl phosphate synthetase or

GMP synthetase increase in neoplasia linked with transformation and progression (Weber 1984).

- Low glutamine concentrations led to morphological, phenotypical and functional differentiation in U937 myelomonocytic cells (Spittler *et al*., 1997). A glutamine dose-dependent change of phenotype and proliferation rate has been observed in human colon carcinoma cell lines Caco-2 and SW62032. Supplementation of glutamine decreases differentiation and diminishes adhesion matrix proteins associated with decreased integrin expression.
- Elevated m-RNA levels of the growth arrest- and DNA damage-inducible genes, GADD45 and GADD153/CHOP (C/EBP-homologous protein), as well as GRP78 (glucose-regulated protein of 78 kDa) was examined in several human breast cancer cell lines subjected to acute glutamine deprivation (Abcouwer *et al*., 1999).
- Neoplasms also depend on glutamine for synthesis of protein and the formation of the precursors of nucleic acids (Knox *et al*., 1967).
- Glutamine transport into the human hepatoma cell line HepG2 is catalyzed primarily by an ASCT2-type transporter (Pollard *et al*., 2002). It was found that both cellular growth rate and ASCT2 expression were significantly lowered by glutamine deprivation (Bungard *et al*., 2004).

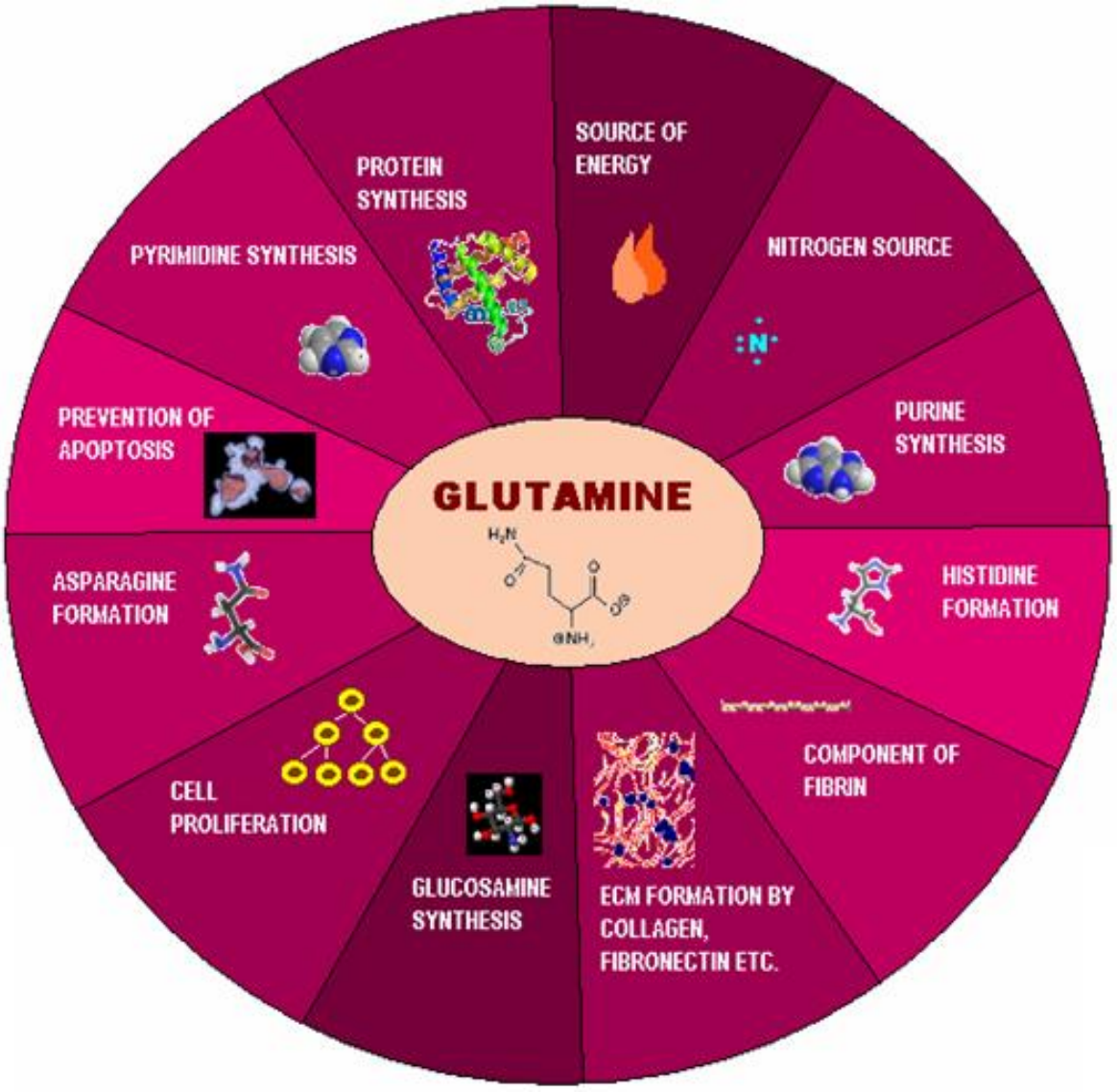

Figure 1: Multifold functions of the non-essential amino acid glutamine.

Role of glutamine in tumor-induced angiogenesis- Angiogenesis is the generation of new capillaries through a process of pre-existing microvessel sprouting. Tumor angiogenesis refers to the growth of new vessels towards and within the tumor. Judah Folkman was one of the first researchers to associate angiogenesis with tumor development (Folkman 1987). Tumor induced angiogenesis is responsible for the nutrition and oxygen supply of the growing tumor while paving way for the elimination of metabolic wastes (Hanahan *et al*. 2000) and can also increase the probability of hematogenous tumor dissemination. Tumors with high vasculature have a higher incidence of distant or node metastasis and a poorer prognosis. Once tumor-induced angiogenesis begins, it continues indefinitely until whole of the tumor is eradicated or until the host dies (Folkman 1985).

Both solid and ascites tumors are characterized by hyperpermeability of blood vessels, extravasation of plasma proteins like fibrinogen, clotting of extravasated fibrinogen to form crosslinked fibrin deposit in the peritoneal lining (Nagy *et al*., 1989).

Fibrin is an extracellular matrix protein of developing tumors (Nagy 1995) and is known to induce angiogenesis (Dvorak *et al*., 1987). The extent and stability of capillary tube formation *in vitro* is markedly affected by the modulation of the fibrin structure (van Hinsbergh 2001). The structure of fibrin is an important determinant of angiogenesis. Both histidine and glutamine are the structural components of fibrin. Glutamine is the donor of amide group which constitutes the imidazole nitrogen molecule of histidine (Neidle 1959) and together they contribute to fibrin formation. This is the reason why glutamine plays special role in the structural organization of fibrin, thus contributing to tumor induced angiogenesis.

Regulation of glutamine metabolism by glutaminase and glutamine analogues- The diverse roles played by glutamine in tumors suggest its inevitable contribution to malignancy. Two glutamine-related antineoplastic therapies have gained much attention since the 1980s. One of them is glutamine clearance by a glutaminolytic enzyme, such as glutaminase and the second is the use of glutamine analogues to kill tumor cells by exhausting their provision of glutamine. Some of the analogues of glutamine which have been tested for their anti-cancer effects include azaserine, 6-diazo-5-oxo-l-norleucine, azotomycin, duazomycin A and acivicin.

CONCLUSION

Several studies on glutamine metabolism in cancer cells is continuously evolving our understanding of the role of this amino acid in cancer. As for example, one of the recent findings reported transition from monolayer culture to anchorage-independent culture due to glutamine requirement (Jiang *et al*., 2016). Different cell lines also exhibit heterogeneity in terms of glutamine requirements ranging from glutamine auxotrophs to those that are capable of survival without exogenous glutamine supplies (Son *et al*., 2013; Timmerman *et al*., 2013). One recent work has demonstrated that imaging glutamine metabolism could predict specific cancer-causing mutations as well as the sensitivity of tumor cells to therapeutic agents targeted towards glutamine metabolism (Rajagopalan *et al*., 2011). Advancement of glutamine-based imaging in clinics might help in distinguishing different tumor subsets. This would in turn facilitate therapeutic regimens against such specific tumors.

Some of the glutamine-related therapies were also shown to have prominent antiangiogenic effects (Roy *et al*., 2005). The enzyme glutaminase, purified from the ascites fluid of ovarian cancer patients was found to reduce serum VEGF levels in tumor-induced mice (Ghosh *et al*., 2004). The glutamine analogue, acivicin, was found to promote melanoma dormancy and reduce associated angiogenic factors alone and also in combination with glutaminase (Roy *et al*., 2007). Combination therapies with acivicin and glutaminase was also found to regulate proliferation and invasive properties of cells cultured *in vitro* (Roy *et al*., 2008). The promising results obtained through early basic studies need re-testing and analysis in different tumor models using newly developed modern research techniques. Currently investigations are going on to target the isoforms of glutamine-metabolizing enzymes that are specifically utilized by cancer cells and not by healthy cells. Thus, a better insight into cancer cell glutamine metabolism has to be obtained through future investigations so that glutamine based anti-cancer strategies can be designed for the benefit of mankind.

Conflicts of Interest: The authors declare no conflict of interest.

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