

Is Glutamine Effective in Enhancing Host Immune Response to Tumors?¹

V. Suzanne Klimberg²

Department of Surgery, University of Arkansas, Fayetteville, AR

EXPANDED ABSTRACT

KEY WORDS: • glutathione • NK cells • breast cancer • glutamine

Glutamine (GLN)³ is a nonessential amino acid, which becomes “conditionally essential” during periods of catabolic stress, when its use exceeds its production. Clinical studies proved the beneficial effects of GLN supplementation in a number of catabolic conditions, including cancer. Previously we have established that supplemental oral GLN reduced tumor growth in experimental breast cancer.

GLN is also a primary fuel for rapidly dividing cells. It has been shown that GLN is necessary for the in vitro growth and function of T lymphocytes and natural killer (NK) cells. NK cells, by virtue of their spontaneous cytolytic activity against tumor cells, have been shown to be important in control of both induction and progression of cancer. In tumor-bearing rats, tumor cells have been shown to act as GLN traps, leading to a net deficit in available GLN and glutathione (GSH). This condition decreases the GLN available to fuel the growth and function of T lymphocytes and NK cells. In in vitro NK cell assays, GSH can substitute for GLN, suggesting that GLN works by increasing intracellular GSH levels. In implantable sarcoma and breast carcinoma rat models, we have demonstrated that daily oral administration of GLN results in a 40% decrease in tumor growth compared with isonitrogenous-fed controls. This decreased tumor growth was associated with a significant increase in arterial GSH levels and a 2- to 3-fold increase in splenic NK cell activity in these animals. When

ketamine was administered to suppress NK cell activity, both the activated splenic NK cell activity and the decreased tumor growth observed in the GLN-treated group were reversed, suggesting that oral GLN supplementation may decrease tumor growth by enhancing NK cell activity through support of host GLN and GSH stores. Further timing studies in a 7,12-dimethylbenz[*a*]anthracene (DMBA) model (known to depress NK cell activity) demonstrated that most of the effect of oral GLN on NK cell levels is late after tumor development. Our long-term goal is to elucidate the molecular mechanisms of GLN-induced inhibition of tumorigenesis.

Supplemental oral GLN may prevent tumor growth through activation of redox-dependent signaling. This hypothesis is based on the observations that 1) oral GLN prevents tumor growth in implantable, as well as DMBA-induced breast and squamous-cell cancer models; 2) oral GLN supplementation inhibits the production of natural anti-oxidant GSH in tumors while enhancing it in normal tissues; 3) oral GLN activates p53 signaling and inhibits PI3K/Akt signaling in a DMBA-breast cancer model.

LITERATURE CITED

1. Todorova VK, Harms SA, Kaufmann Y, Luo S, Luo KQ, Babb K, Klimberg VS. Effect of dietary glutamine on tumor glutathione levels and apoptosis-related proteins in DMBA-induced breast cancer of rats. *Breast Cancer Res Treat.* 2004;88(3):247–56.
2. Todorova VK, Harms SA, Luo S, Kaufman Y, Babb KB, Klimberg VS. Oral glutamine (AES-14) supplementation inhibits PI-3k/Akt signaling in experimental breast cancer. *J Parenter Enteral Nutr.* 2003;27(6):404–10.
3. Johnson AT, Kaufmann YC, Luo S, Todorova V, Klimberg VS. Effect of glutamine on glutathione, IGF-I, and TGF-beta 1. *J Surg Res.* 2003;111(2):222–8.
4. Klimberg VS, Kornbluth J, Cao Y, Dang A, Blossom S, Schaeffer RF. Glutamine suppresses PGE2 synthesis and breast cancer growth. *J Surg Res.* 1996;63(1):293–7.
5. Kaufmann Y, Kornbluth J, Feng Z, Fahr M, Schaeffer RF, Klimberg VS. Effect of glutamine on the initiation and promotion phases of DMBA-induced mammary tumor development. *J Parenter Enteral Nutr.* 2003;27(6):411–8.
6. Fahr MJ, Kornbluth J, Blossom S, Schaeffer R, Klimberg VS. Harry M Vars Research Award. Glutamine enhances immunoregulation of tumor growth. *J Parenter Enteral Nutr.* 1994;18(6):471–6.

¹ Published in a supplement to *The Journal of Nutrition*. Presented during a workshop entitled: “Immunonutrition: Enhancing Tumoricidal Cell Activity,” held in Bethesda, MD, March 23, 2005. This workshop was sponsored by the Division of Cancer Prevention, NCI, NIH, DHHS. Guest editors for the supplement publication were Susan S. Percival, John A. Milner, and Christopher A. Jolly. *Guest Editor Disclosure:* Susan S. Percival: no relationships to disclose; John A. Milner: no relationships to disclose; Christopher A. Jolly: received reimbursement for travel expenses from NCI.

² To whom correspondence should be addressed.
E-mail: klimbergsuzanne@uams.edu.

³ Abbreviations used: DMBA, 7,12-dimethylbenz[*a*]anthracene; GSH, glutathione; GLN, glutamine; NK, natural killer.