Investigations of Branched-Chain Amino Acids and Their Metabolites in Animal Models of Cancer¹–³

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ABSTRACT Many of the features of BCAA metabolism in the tumor-bearing state are similar to the other disease states that feature involuntary weight loss and skeletal muscle atrophy. These states are generally characterized by altered BCAA availability (low BCAA intakes, elevated rates of BCAA oxidation, and gluconeogenesis), which are concurrent with activation of proteolysis and suppression of protein synthesis in skeletal muscle and ultimately lead to erosion of lean tissue mass. These features in turn imply BCAA deficiency compared with whole-body requirements and are the basis of suggestions for dietary supplementation with BCAA or their metabolites. Recent studies on BCAA supplementation in cancer focus on leucine and its derivative, β-methyl-β-hydroxybutyrate, as regulators of skeletal muscle metabolism, although their relative efficacy is unknown. However, what would otherwise be a relatively straightforward consideration of amino acid supply and demand is confounded by the presence of the tumor and its potential utilization of BCAA for its proliferative and invasive activities. Positron emission tomography with ¹¹C-leucine, used for in vivo tumor imaging, points to the high avidity of tumor amino acid uptake. These features have incited research in opposing directions, probing BCAA deprivation, with a view to limiting tumor growth, as well as BCAA supplementation, with a view to supporting maintenance of host lean tissue. No clear conclusion is presently available from the sum of these efforts. Animal models with relevant clinical features are essential to determine if amino acid therapy can alter the balance between the host and the tumor in a manner that favors the host overall. J. Nutr. 136: 237S–242S, 2006.

KEY WORDS: • amino acids • tumor • cachexia • supplementation • muscle wasting

Cancer cachexia and amino acid metabolism

The majority of patients with cancer will experience malnutrition and involuntary weight loss known as the cachexia-anorexia syndrome. This syndrome is a major contributing cause to morbidity and death in up to 50% of patients with advanced cancer (1). The mechanisms of cancer cachexia are complex; however, alterations in protein and amino acid metabolism appear to play a major role (2). Several factors, which also occur in other disease states (i.e., 3), contribute to alterations in amino acid metabolism in cancer, including reduced dietary intake, increased oxidation of branched-chain amino acids (leucine, isoleucine, and valine), and net catabolism of skeletal muscle through a reduction in protein synthesis and activation of proteolysis. Proinflammatory cytokines and glucocorticoids are some of the key factors responsible for systemic activation of the changes in amino acid metabolism that occur in the diseases that result in cachexia. Although the metabolism of BCAAs in cancer cachexia includes common features with other disease states, the role of tumor metabolism and tumor-derived mediators that can alter amino acid demand and metabolism is unique to cancer. The BCAAs are central in the maintenance of lean body mass and regulation of skeletal muscle protein metabolism; thus, it is important to examine the metabolism of BCAA in the tumor-bearing state, where muscle wasting is prominent.

BCAA balance in the tumor-bearing state

The net balance of BCAA is the difference between supply and demand. In the tumor-bearing state, as well as other catabolic states, there appears to be an increase in BCAA demand that is not met by BCAA supply. Dietary intake and amino acid release from protein degradation are the only supplies of the essential BCAA. Demand for the BCAA is primarily
for protein synthesis; however, oxidation for energy production can contribute to BCAA utilization. BCAA catabolic losses are mediated by an oxidative pathway that starts with BCAA aminotransferase (BCAAAT) and is followed by the first irreversible step catalyzed by branched-chain \( \alpha \)-ketoacid dehydrogenase (BCKDH). Regulation of the activity state of BCKDH by way of its kinase and its phosphatase is critically important in overall BCAA balance (4,5). The tumor models described in Table 1 have been used to define these elements of BCAA balance.

### Amino acid utilization by the tumor

#### Tumor BCAA uptake and metabolism.

The unique feature of cancer as a disease is the capacity of the disease itself to use amino acids for its own metabolism and for its proliferative and invasive activities. Thus, the balance sheet of whole-body amino acid metabolism must include a quantitative as well as a qualitative understanding of tumor amino acid utilization. Like nontumor tissue, it seems apparent that tumors utilize BCAA for protein synthesis and may to some extent oxidize them either partially or completely. For example, both the Walker 256 carcinosarcoma and Morris hepatoma 5123 have activity of BCAAAT per gram protein is less than that of skeletal muscle in tumor-bearing rats (9,15). However, BCKDH activity in the tumor per gram protein is higher than tumor-bearing rat muscle in the Morris hepatoma but less in the Walker 256 (9,15), suggesting that some tumors may have a higher capacity for BCAA catabolism than others. These features of tumors have not been systematically studied.

Information on amino acid transport in tumors has been examined in malignant cell lines. The uptake of leucine by C6 glioma (24) and breast cancer cell lines MDA-MB-231 and MCF-7 (25) is by a system L inhibitor–sensitive, sodium-insensitive, \( L \)-type amino acid transporter (LAT1). LAT1 mRNA was ~200 times more abundant than LAT2 mRNA in MCF-7 cells, MDA-MB-231 cells express LAT1 but not LAT2 mRNA, and C6 glioma cells express LAT1 in contrast with normal astrocytes, which mainly express LAT2. These differences have been proposed as a useful basis for the differential identification of tumor tissue versus nonmalignant adjacent tissue (i.e., tumor margin). Work on the kinetic features of these transporters may account for any differential BCAA uptake compared with normal tissue.

Preferential uptake of amino acids by tumors is very nicely demonstrated in vivo by amino acid positron emission tomography (PET), a methodological approach that has been applied for a little over 15 y to visualize metabolic activity of tumor tissue. Amino acid PET has emerged as being particularly strong in the imaging of brain tumors. Positron-emitting isotopes \( ^{18}F \) and \( ^{11}C \) have been incorporated into methionine, tyrosine, phenylalanine, tryptophan, valine, and leucine. For example, the uptake of valine in a rat brain tumor model was shown to be 22-fold higher than in contralateral brain cortex, whereas the uptake of \( ^{18}F \)-deoxyglucose was only 1.5-times higher, suggesting that an amino acid tracer would display a much higher differential signal in tumor versus nontumor tissue than would glucose (26). Ishiwata and coworkers (8) compared brain and tumor uptake of labeled methionine, leucine, and tyrosine in mice bearing carcinomas in order to compare the potential for the use of positron-emitting analogs of these amino acids in brain tumor imaging. These authors concluded that because a higher proportion of leucine than other amino acids appeared in the acid precipitable fraction (i.e., was used for protein synthesis), then leucine would be preferable to other amino acids for tumor labeling. The use of \( ^{18}F \) or \( ^{13}C \) amino acid analogs for clinical tumor imaging demonstrates the avidity of tumor uptake of amino acids compared with other tissues. Knowledge of this high uptake causes a natural tendency by various investigators to assume that this translates to an ability of tumors to compete for amino acid supplies more effectively under conditions of supplementation. However, this key question remains to be substantiated.

PET-based approaches using \( L^{-1-^{13}}C \) leucine have been elegantly validated for measurement of regional rates of protein synthesis in the brain in a monkey model (27), allowing for accurate and reproducible measurement of protein synthesis. These approaches might well be applied for analysis of the differential utilization of supplemented amino acids, in such a manner as to clarify which tissues capture these most effectively.

#### Factors affecting amino acid utilization by tumors

There are very few quantitative data available in the literature regarding tumor amino acid uptake and metabolism; however, it may be conjectured that the following key features of the tumor will influence its relative use of BCAA.

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**Table 1**

<table>
<thead>
<tr>
<th>Tumor BCAA uptake and metabolism.</th>
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<td><strong>Characteristics of the animal tumor models used in the examination of BCAA metabolism</strong></td>
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<tr>
<td><strong>Tumor</strong></td>
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<td>MAC16 adenocarcinoma</td>
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<tr>
<td>Mammary tumors:</td>
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<tr>
<td>MRRMT-1</td>
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<tr>
<td>FM3A</td>
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<td>Morris hepatoma 5123c</td>
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<td>7777</td>
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<tr>
<td>RNC 254 fibrosarcoma</td>
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<td>Walker 266 carcinosarcoma</td>
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<td>Ascites hepatoma:</td>
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<td>Yoshida AH 130</td>
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<td>AH 109A</td>
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<td>Yoshida sarcoma</td>
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1. PIF, proteolysis-inducing factor; S-D, Sprague-Dawley; * not well characterized as a cachexia model.

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**Abbreviations used:** BCAAAT, branched-chain amino acid aminotransferase; BCKDH, branched-chain \( \alpha \)-ketoacid dehydrogenase; HMB, \( \beta \)-hydroxy-\( \beta \)-methylbutyrate; LAT1, \( L \)-type amino acid transporter; LNAA, large neutral amino acid; PET, positron emission tomography; PIF, proteolysis-inducing factor.
Primary histological type. The principal issue of importance here may be whether a given tumor stems from a tissue with capacity to oxidize BCAA in the first place. Recent works focusing on tissue distribution of BCKDH activity (28) have shown that this activity is located in a few surprising places. It also seems likely that the characteristic state of differentiation of a tumor may relate to a capacity for BCAA oxidation.

Aggressive versus indolent tumors. Protein biosynthesis is a primary determinant of tumor amino acid use and will implicate all 20 amino acids used in this process. The fractional synthetic rate of protein of tumors is high relative to other tissues in the tumor-bearing animal (29). The fractional synthesis rate of colorectal tumors in humans were in the ranges of 17.2–33.9% per day, and in breast tumors the range of rates obtained was 5.3–15.9% per day (30). The impact of this amino acid use will depend on specific tumor type and physiological characteristics, including synthetic rate, mass, and rate of proliferation.

Tumor burden. We have estimated that a Morris hepatoma 7777 in rats, at 0.2% of body weight, captures 2.0% of the animal’s daily nitrogen balance (10). Notably, this represents a 10-fold difference between the expected nitrogen capture by the tumor based on its mass versus its actual metabolic activity. At higher tumor burdens the tumor represents a significant nitrogen trap. For example, for a tumor representing 8.8% of body weight, the daily nitrogen balance of the tumor is equivalent to 150% of the daily retention of nitrogen from the diet (10). Because few detailed balance studies exist, the quantity of amino acid capture by most tumors is unknown.

Most tumor models are employed under conditions of unrestricted tumor growth at sites of subcutaneous implantation to eventual tumor burdens of up to 30% of body weight. In humans, tumors develop at an organ site (such as the colon, lung, or brain) and are usually fatal at very limited tumor burden (i.e., 1–2% of body weight). Failure to pay attention to this difference is the principal weakness of studies where quantitative aspects of amino acid metabolism have been studied in animal models. In the presence of unrestricted tumor growth, the tumor becomes a significant site of mass capture of amino acids and a quantitatively important reason for depletion of physiological amino acid pools. At some point, experimental tumors capture amounts of amino acids far greater than could ever be expected in a typical human cancer. It is thus possible to easily generate a state of severe deficiency of BCAA in an animal model, but it is at present impossible to understand which (or whether any) of these animal models accurately represents the characteristic state of differentiation of a tumor.

Systemic effects induced by tumors or treatments that influence BCAA balance

Anorexia: inducing or not. Tumors used in animal models may or may not induce anorexia, and if they do have this effect, they do so to varying degrees (Table 1). The MAC16 adenocarcinoma is a cachexia model with no associated anorexia in spite of profound wasting of apparent metabolic origin; most other models express some degree of anorexia (31).

Inflammation: inducing or not. Chronic inflammation can affect amino acid availability for the reason that proinflammatory cytokines stimulate hepatic protein synthesis as a part of the acute phase response that includes the synthesis of specialized plasma proteins called acute phase proteins. Proinflammatory cytokines also induce BCKDH (32). An inflammatory response is common in several types of human cancers, including pancreatic (33), lung (34), and colon (35), as well as a wide variety of animal models (Table 1). Inflammation is associated with weight loss and shortened survival (36–38).

Antineoplastic therapy. One of our perennial criticisms of the literature on amino acid nutrition in animal models of cancer is that they almost invariably consider only the situation of unrestricted tumor growth in the absence of therapy. It is conceivable that treatments (particularly chemotherapy treatments) may alter amino acid supply and demand in their own right. For example, the injury done by chemotherapy to non-tumor tissues, such as intestinal epithelium and bone marrow, obviously entails some nutritional demands. The effect of chemotherapy treatment on the overall balance statement for amino acid supply remains to be determined.

Alterations in BCAA supply and demand in the tumor-bearing host

Dietary intake of BCAA in the tumor-bearing state. A loss of appetite resulting in an overall reduction in dietary intake in advanced cancer patients is a frequent observation (39). Animal tumor models may also feature a reduction in food intake, although anorexia in these models may be absent or present (Table 1) and can vary considerably. For example, with the rapidly growing Yoshida ascites hepatoma 130, food intake is reduced rapidly over 7 d of tumor growth, whereas food intake in the MAC16 model is not reduced (31). Therefore, there is a discrepancy in overall dietary intake between models, which has implications on BCAA supply. In addition, the impact of tumor and antineoplastic therapy on absorption of BCAA is not well understood and may play a role in altering BCAA supply.

Some authors have suggested that an additional degree of anorexia may be secondary to a reduction in BCAA supply (40). This is thought to occur through competitive inhibition for blood–brain barrier transport and subsequent modification of neurotransmitter synthesis. Enhanced skeletal muscle breakdown results in the release of aromatic amino acids that are not metabolized within the muscle, relative to BCAA, creating a high aromatic:BCAA ratio in peripheral blood. This may result in an increased blood–brain barrier transport of the aromatic amino acids and an increase in the aromatic amino acid–derived neurotransmitters. Serotonin in particular may play a role in the development of anorexia. Cangiano et al. (41) provided weight-losing cancer patients with a BCAA supplement for 7 d and demonstrated that these patients had a higher plasma concentration of large neutral amino acids (LNAs) and a lower tryptophan:LNAA ratio than cancer patients given an isonitrogenous supplement (41). Because the changes in amino acid levels corresponded with an increase in spontaneous caloric intake, the authors hypothesized that by increasing BCAA plasma concentrations, the transport of tryptophan across the blood–brain barrier was decreased resulting in less serotonin synthesis (41).

Protein synthesis and degradation in the tumor-bearing state. Negative nitrogen balance and skeletal muscle wasting indicate that overall protein catabolism is greater than anabolism in cancer cachexia (42). Activation of skeletal muscle protein degradation through the ATP–ubiquitin pathway is induced by both host and tumor-derived mediators (43). Meanwhile, skeletal muscle protein synthesis is either unchanged or reduced, which results in a net loss of skeletal muscle protein (43). Because myofibrillar proteins are composed of ~18% BCAA, acceleration of skeletal muscle protein breakdown is associated with mobilization of these amino acids, although they also tend to be catabolized within muscle tissue (see below).

BCAA oxidation in the tumor-bearing state. Leucine oxidation and the activity of BCAAT and BCKDH have been examined mainly in the Walker 256 tumor model. Whole-body
in vivo leucine oxidation is elevated 2- to 3-fold in Walker 256-bearing rats at tumor burdens of 3–20% body weight (12,13). At a tumor burden of 4% of body weight, leucine oxidation in isolated soleus muscle Walker 256-bearing rats was elevated 1.5-fold, whereas leucine incorporation into muscle tissue was unchanged compared to nontumor-bearing controls (12). At a higher Walker 256 tumor burden (19% body weight), isolated extensor digitorum, but not soleus, muscle had an increased release of tyrosine by 1.3-fold and leucine oxidation by 2.8-fold (14), indicating that elevated skeletal muscle protein breakdown is associated with the increase in leucine oxidation. Similarly, rats bearing the Yoshida ascites hepatoma 130 had elevated rates of whole body (1.3-fold) and in vitro soleus muscle (2-fold) leucine oxidation, which was associated with a reduction in leucine incorporation into muscle protein (20). Increased intramuscular activity of the BCAAT and BCKDH enzymes occurs in the Walker 256 tumor (13,15); however, liver activity of these enzymes is not affected (15), suggesting that muscle leucine oxidation plays the greater role in the elevated rates of whole-body leucine oxidation. The studies in the Walker 256 model are in agreement with another tumor model (Morris hepatoma 5123) in which the amount of administered [14C]-leucine was oxidized on the whole-body level at a tumor burden of 9% body weight compared with nontumor-bearing controls, which was associated with increased BCKDH activity in muscle and kidney from tumor-bearing rats (9). Although hepatic BCKDH activity was not affected by the Morris hepatoma 5123 tumor, BCAAT activity was doubled. Thus, like other catabolic states, the enzymes involved in the initial steps of BCAA degradation have increased activity and result in elevated rates of leucine oxidation within muscle and at the whole-body level.

Activation of muscle protein catabolism and of the BCKDH complex is part of an essential physiological function serving to provide carbon for gluconeogenesis during fasting. BCAA oxidation within muscle provides nitrogen for the synthesis and release of gluconeogenic amino acids, especially glutamine and alanine. Weight-losing cancer patients demonstrate increased rates of gluconeogenesis that are not suppressed by glucose provision (44,45). Glucose utilization in tumor cells as an energetic fuel and alterations to host metabolism are possible means by which the presence of a tumor may signal BCAA catabolism. In addition, under conditions of energy deficit, such as in cancer cachexia, this may be beneficial in the production of energy within muscle.

Amino acid therapy in malignant disease

Research in this area is centered on the concept of manipulating amino acid supply in a manner that alters the balance between the host and the tumor and favors the host overall. However, the approaches taken around this concept come from opposing directions. Some researchers have approached this from the perspective of selective BCAA amino acid depletion, with a view to injuring the tumor to a greater extent than the host. Others favor the idea of selective BCAA supplementation in the hope of overall benefit to the host with hopefully little or no advantage conferred to the tumor. At some fundamental level these approaches are related and go back to Harper's concept of amino acid imbalance (46). What remains unknown at this time is to what extent tumor-specific and host processes are saturated at prevailing BCAA levels in physiological pools in the tumor-bearing state so as to be able to predict the net outcome of BCAA supplementation or depletion.

**Selective amino acid depletion.** With elevated amino acid uptake and utilization in tumors, an approach to anticancer therapy may potentially be based on the specific inhibition of amino acid uptake by tumors. This concept was applied in animal models during the early 1990s using dietary restriction of specific amino acids (arginine and methionine) or anti-metabolites interfering with glutamine metabolism (47–49). Experimental ascites hepatoma AH-109A has been demonstrated to be sensitive to dietary deficiency of BCAA, especially valine, which causes remarkable reduction (~70%) in tumor growth (7). This approach remains poorly substantiated, and it is unknown whether differential sensitivity to valine depletion (or that of any other amino acid) is a generalized feature of malignant cells or highly specific to certain tumor types. Even if valine depletion therapy does seem to suppress growth of the AH-109A tumor, it has some serious drawbacks. As a category, this “starve the tumor of amino acid” approach also starves the host of essential amino acids, resulting in reduced protein synthesis and nitrogen balance overall, and fatty liver occurs due to the differential suppression of the synthesis of hepatic apolipoproteins essential for lipid export from hepatocytes (22). On balance, for selective amino acid depletion to be effective, means of circumventing systemic effects on host tissues would need to be devised.

**Selective BCAA supplementation.** Much of the BCAA supplementation work emanates from the understanding that leucine promotes global protein synthesis by signaling an increase in translation, promotes insulin release, and inhibits autophagic protein degradation. A strong case can therefore be made that the proper leucine concentration in the various compartments of the body is critically important for maintaining body protein levels beyond simply the need of this essential amino acid for protein synthesis. The conjecture is that protection of body protein during illness and stress may be improved by therapeutic control of BCAA supply; however, the current weakness that stems from this approach is that these protein synthetic effects may concomitantly extend to the tumor and increase its proliferation, growth, or metastatic potential.

**Parenteral supplementation with isoleucine, leucine, and valine.** Supplementation with BCAA has focused on the provision of all three BCAAs parenterally in cancer patients. Weight-losing cancer patients with various intra-abdominal adenocarcinomas had higher leucine balance, increased protein synthesis, and elevated rates of albumin synthesis when given a parenteral nutrient solution containing 50% BCAA compared with a standard solution containing 19% BCAA (50,51).

Unlike other stress conditions in which BCAA supplementation has been used to improve protein balance, a concern in the tumor-bearing state is that provision of nutrients, including amino acids, will promote tumor growth by increasing protein synthesis (52). This may be less serious a concern with BCAA than with other amino acids that are more involved with cell synthesis (52). This may be less serious a concern with BCAA than with other amino acids that are more involved with cell synthesis (52). This may be less serious a concern with BCAA than with other amino acids that are more involved with cell synthesis (52). This may be less serious a concern with BCAA than with other amino acids that are more involved with cell synthesis (52).
protein synthesis is increased in the tumor-bearing state (11). Parenteral provision of a solution containing 50% BCAA to rats bearing the Yoshida sarcoma reduced tyrosine oxidation and increased hepatic protein synthesis compared to tumor-bearing rats receiving a solution containing 19% BCAA (23). Also, no changes in tumor volume, weight, synthetic rates, degradation rates, or growth rate were observed with the higher BCAA administration (23).

Supplementation with leucine. Leucine alone has been examined as a supplement to improve protein balance and lean body mass because of its role in regulation of protein synthesis and degradation. Rats bearing the Walker 256 tumor had higher lean body mass, gastrocnemius weight, and myosin content when fed a diet containing 15% protein and 3% leucine compared with tumor-bearing rats fed a diet containing 18% protein and no additional leucine, but the additional leucine did not affect tumor growth (16). Leucine supplementation has also been studied in pregnant rats bearing the Walker 256 tumor. Pregnancy induces an additional metabolic demand that would compete with tumors and with maternal tissues for amino acids. Pregnant tumor-bearing rats fed a standard diet containing 18% protein not only exhibited a reduction in maternal protein balance, but fetal weight was also decreased by 50% compared with nontumor-bearing pair-fed controls, indicating that the tumor developed at the expense of maternal protein reserves and fetal development (17,18). The provision of supplemental leucine (15% protein and 3% leucine) increased maternal lean body mass, noncollagen nitrogen content, and muscle protein synthesis and lowered muscle protein degradation, but the additional leucine did not increase either tumor or conceptus growth (17,19). These results in pregnant animals imply that tumor-related processes are already saturated for BCAA supply under basal conditions and that additional supplies of BCAA are directed to nontumor processes, especially skeletal muscle tissue. Because additional leucine provision did not alter tumor mass or fetal growth, leucine supplementation may act on skeletal muscle protein balance by an independent mechanism that does not increase protein synthesis in general.

Regulation of skeletal muscle degradation by leucine and its metabolites. Incubation of muscle from healthy rats in medium containing leucine lowers proteolytic rate, whereas muscle from rats bearing the Yoshida ascites hepatoma do not respond to leucine (21). The addition of leucine lowers the expression of some of the components of the ATP-ubiquitin proteolytic pathway; however, it was less effective in tumor-bearing rats compared to nontumor-bearing rats (21). The diminished effect of leucine on skeletal muscle proteolysis in the catabolic state may be related to the induction of protein breakdown by host or tumor-derived mediators. Another possibility is that a leucine metabolite that inhibits muscle protein degradation (54) may be altered in the tumor-bearing state.

An alternative pathway for α-ketosacaproic acid is oxidation to β-hydroxy-β-methylbutyrate (HMB) by α-ketosacaproate dioxygenase (55). A study in lambs and pigs demonstrated that HMB production accounts for 2–10% of leucine oxidation in the postprandial state, and a portion of HMB is metabolized (55). Supplementation with HMB, in combination with glutamine and arginine, was claimed to achieve moderate lean body mass gains in weight-losing advanced cancer patients, although this was a small study in which many patients died during the study period (56).

The addition of HMB to the medium of cultured C2C12 myotubes reduces proteolysis induced by the tumor-derived proteolysis-inducing factor (PIF) (57). Administration of HMB (0.25 g/kg) in mice bearing the PIF-producing tumor MAC16 reduced muscle proteolytic rates through an attenuation of the ATP-ubiquitin–dependent pathway, including protein levels of 2OS subunits, 19S subunits, and E214k (6). Thus, supplementation of HMB may be more effective than leucine in reducing proteolysis in the tumor-bearing state because increased leucine oxidation through the BCKDH pathway may prevent or lower the production of HMB from α-ketosacaproate.

In summary, amino acids, including BCAAs, are simultaneously the precursors and substrates essential for tumor growth and for the physiological functions of the tumor-bearing host. Each and every organ, tumor, and function therein can be considered to have a characteristic dose responsiveness to amino acid supply. The few data available on BCAA in the tumor-bearing state suggest that the dose responsiveness of tumor and host functions may be differential (i.e., that tumors may be more sensitive to amino acid depletion than host tissues or that host tissues capture more of amino acids supplemented in the diet than do tumor tissues). It can thus be suggested that there must exist an ideal level of amino acid supply that maximizes advantage to the tumor-bearing host during its battle for survival of malignant disease. The challenge will be to find an experimental approach to identify this crucial balance point.

LITERATURE CITED