MINIREVIEW

Interchange of Amino Acids between Tumor and Host

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During the growth of a tumor, there are very relevant changes in the metabolism of the host to produce the metabolites rapidly consumed by the tumor. In this context, the exchanges of amino acids between the tumor and its host are especially important; however, they have received little attention. A rigorous study must provide data on the growth curve of the tumor, as well as on amino acid levels in tumor cells, plasma, and metabolically relevant tissues and organs from the host during the whole growth of the tumor. The main conclusions arising from a complete study in a tumor model are discussed.

The metabolic interactions between host and tumor are not yet well understood and they have received little attention (1). Neoplastic transformation is accompanied by an adaptation of metabolism to an increase in nucleotide and protein synthesis. The high rates of protein synthesis in rapidly growing tumors require a continuous supply of both essential and nonessential amino acids (2–4). Mider (5) showed that tumors assimilate not only the nitrogen from the diet, but also the nitrogen proceeding from host proteins. In this way, tumors can be considered as "nitrogen traps," actively competing with their host for nitrogen compounds (6). Tumors use the incorporated amino acids not only for protein synthesis but also for oxidation (7). For this reason, the presence of a growing tumor has a pronounced effect on the nitrogen metabolism of the host tissues, such as muscle (8) and liver (9).

Amino acids from host tissues are delivered to the tumor cells through blood vessels. Thus, the plasma free amino acid pool can be considered to be the main direct source of those amino acids for the tumor. However, in contrast with other pathological situations, a characteristic pattern of the plasma amino acids in neoplastic conditions has not been found (10–13). As Felig (14) indicates, the plasma free amino acid concentrations under normal conditions show relatively little intra- or interindividual variations; they are maintained at constant levels by a net balance between the metabolic amino acid uptake and release by the tissues. This balance
can be perturbed in the presence of a tumor by a number of different means: (i) by variations in the ingested protein (15); (ii) by changes in the intestinal absorption (15); (iii) by alterations of the nonessential amino acid biosynthesis in liver (16); (iv) by changes in tissue oxidative breakdown of amino acids (17); (v) by the differences between protein synthesis and tissue proteolytic activities (18); and (vi) by tumor demand for the essential and nonessential amino acids needed for tumor proliferation (19). Consequently, it is extremely difficult to attribute the observed variations of plasma amino acid concentrations specifically to one or more of the metabolic processes mentioned. Several attempts have been made by different groups to study amino acid variations in the plasma of cancer patients and tumor-bearing animals (20–22). Nevertheless, as Kawamura et al. (2) point out, these experiments were single observations at a moment, without regard for the stage of tumor development and, as Krause et al. (23) discuss, this kind of measurement could be largely anecdotal. Rivera et al. (24) made a complete study of amino acid contents in liver and muscle of nontumor-bearing and tumor-bearing mice, as well as a study of amino acid contents in the tumor 15 and 25 days after tumor implantation. However, these authors did not give any data on tumor growth; furthermore, the 25th day is only 2 to 4 days before mouse death and a number of secondary phenomena, such as cachexia (25) and/or hyperammonemia (26) contribute to obscure the complete picture. Actually, the main changes in host metabolism directly elicited by tumors occur shortly after tumor inoculation, and they can be observed 24 h after inoculation (26).

Consequently, it appears that a valid study (in a tumor model) of the overall amino acid movement and interchange between host and tumor requires (i) the establishment of the growth curve for the tumor, (ii) the study of amino acid levels in tumor at different stages of the growth curve; and (iii) the study of amino acid contents in plasma and metabolically relevant tissues and organs from the host (i.e., liver, or muscle) at different days during life span, even before tumor growth starts to be relevant. To our knowledge, up to now there is only one complete study fulfilling these requirements and this is a study of amino acid exchange between Ehrlich ascites tumor cells and the host mice carried out in our lab (9,27,28). Taking the reports of this work as the main references, and quoting significant data from other published papers, it appears that it is not possible to find a common profile in the variations of the amino acid concentrations in plasma during tumor development. However, several analogous patterns for specific groups of amino acids can be considered. In the rest of this paper, these different patterns are briefly commented upon.

Glutamine, Asparagine, and Serine

These three nonessential amino acids behave as essential for the tumor cells: their concentrations in ascitic fluid is always lower than in plasma, reflecting a net flux from host tissues to tumor (27).

In tumor cells, there is an increase in the activities of the enzymes involved in serine biosynthesis, as well as an increase in the activities of the enzymes that use serine as a precursor for purine biosynthesis (29–31). The consumption of
serine by tumor cells produces a decrease in the concentration of this amino acid in host tissues, even shortly after tumor inoculation (9,24).

On the other hand, tumor glutaminase and asparaginase are very active (32,33). Nonetheless, there is a special and significant increase of plasma glutamine concentration during the first days of tumor growth, reflecting the simultaneous modulation of glutamine synthetase and glutaminase activities in liver and kidney, conducive to a net production of glutamine by the host tissues (9,26). There is a wide consensus that glutamine is the main vehicle of nitrogen between the host and the tumor (14,34). In tumor cells, in the middle of the exponential growth phase, glutamine is undetectable, as also occurs in the case of the essential amino acids leucine and arginine (27). The importance of the changes in host glutamine metabolism elicited by tumors and that of the glutamine metabolism in tumor cells have been recently stressed in an extensive review (35).

**Acidic Amino Acids**

Glutamate and aspartate are the first products in the glutaminolytic and asparaginolytic pathways (33,36), and they are the main end products of glutamine metabolism in Ehrlich ascites tumor cells (37). The net flux of these amino acids observed from tumor to host plasma (27) requires no further explanation. In tumor cells at the stationary phase of growth, the concentration of glutamate rises to 7.8 mM (27). In both batch and continuous perfusion in the presence of glutamine, glutamate is produced and extruded by tumor cells (33,38).

**Alanine, Glycine, and Proline**

These three nonessential amino acids are always present in the plasma at high concentrations and there is a net flux from tumor cells to plasma. This flux is maximum during the plateau phase of tumor growth (27). Alanine can be produced by tumor cells de novo from glutamine and glucose (39). During both exponential and plateau phases of tumor growth, the concentrations of these three amino acids are the highest in tumor cells (27). On the other hand, it is noteworthy that the high concentrations of proline and glycine found in the ascitic fluid might result from the action of a tumor collagenase on the extracellular matrix surrounding the tumor cells (40).

In the liver of tumor-bearing mice, alanine concentration remained lower than in the liver of control mice during almost the whole period of tumor growth. In contrast, proline concentration increased on the 7th day after tumor transplantation, that is, in the exponential growth phase. These results are consistent with the observations in tumor-bearing mice that alanine is a good gluconeogenic substrate and that the liver is somehow impaired to metabolize the excess of proline supply (9).

**Sulfur Amino Acids**

Methionine participates in three processes: protein synthesis, polyamine synthesis, and transmethylation reactions (41). S-Adenosylmethionine decarboxylase activity is strongly stimulated in Ehrlich ascites cells, simultaneously with the tumoral DNA synthesis (42). As an essential amino acid, plasma methionine...
concentration decreases during the first days of tumor growth and there is a net flux from the host to the tumor during the latent, exponential, and plateau phases of Ehrlich ascites tumor cell growth (27). At the same time, a significant decrease in the liver methionine concentration is observed (9).

Plasma and liver cysteine concentrations significantly increase in the tumor-bearing animals (9,27), although at the same time, tumor cells can also store this amino acid (27).

Pine et al. (20) describe an accumulation of taurine in mice mammary tumors, which is consistent with the capacity for storing taurine observed in Ehrlich cells (27).

**Branched-Chain and Aromatic Amino Acids**

The nonessential amino acid tyrosine, and the essential amino acids leucine, isoleucine, valine, tryptophan, and phenylalanine share common features with the other essential amino acids; i.e., there is a sharp decrease in their plasma and liver concentrations 48 h after tumor inoculation (9,27). This is most probably due to the high increase in the liver protein synthesis detected during this period (24,43), and there exists a net flux from host tissues to tumor (27).

**Cationic Amino Acids**

Arginine, histidine, and lysine show a similar behavior to the other essential amino acids (27). It is noteworthy that arginine is the only amino acid not detected at the plateau phase of growth in Ehrlich cells (27). In rodent mammary adenocarcinomas, arginine pools can also be depleted (20). The decrease of the arginine concentration in ascitic fluid and the lack of free intracellular arginine are not surprising since this amino acid should be avidly consumed by the tumor cells as a source of ornithine needed for its accelerated polyamine biosynthesis (44). In fact tumor arginase and ornithine decarboxylase activities are very high (28). Although tumors were claimed to exert a suppressive effect on liver arginase activity (11,45), in Ehrlich ascites tumor-bearing mice a two- to three-fold increase in liver arginase activity is observed (28).

A high correlation was found between polyamine biosynthesis, ornithine decarboxylase, and the growth rate in tumor cells. The active polyamine synthesis requires a supply of ornithine from the host. Ornithine concentration increased in plasma after tumor transplantation. A gradient of ornithine was maintained between plasma and ascitic fluid. In this way, ornithine also behaves as an essential amino acid for tumor (28). Liver seems to be a source of additional supply of both ornithine and polyamines. In fact, liver content of ornithine is minimum during the exponential and plateau phases of tumor growth, when liver ornithine decarboxylase is increased (28).

**The Special Case of Threonine**

Threonine is always listed as an essential amino acid; however, the observed concentration gradient seems to indicate a net flux from the tumor cells (27). Sauer et al. (10) also report that Walker 256 carcinomas release threonine together with glycine, alanine, and aspartic acid in order to increase the net glucose pro-
duction in the host. Very little information is available on the metabolism of threonine and further investigation is needed to determine if threonine is produced in tumors de novo.

Concluding Remarks

It should be stressed that the patterns discussed in this paper are those occurring during latent, exponential, and plateau phases of tumor growth. The picture becomes almost chaotic in the last days of life span, making it very difficult to discuss the results because a complex interplay of many factors brings about the death of the host.

The study on the overall amino acid movement and interchange between host and tumor should be completely carried out in other tumor models to compare them with the works carried out in Ehrlich cells (9,27,28). This would make possible a comparison to detect eventual common behaviors or to discriminate if differences in the behavior of marker amino acids correlate with malignancy, metastatic capacity, or other oncological properties.

REFERENCES


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