Hypothesis

Tumour-host metabolic interaction and cachexia

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Cachexia is a terminal metabolic problem observed in a wide variety of tumours. In this article I propose that the syndrome is a direct consequence of the common feature to all malignant tumours: growth. I suggest that the requirement for essential amino acids can be used as the unifying principle that links the tumour to the two main components of cachexia: muscle wastage and anorexia. This underlying factor is usually clouded by the overlapping of individual tumour characteristics.

Amino acid *Cancer* *Cachexia* *Metabolism* *Growth*

1. INTRODUCTION

Cachexia is the most common general metabolic syndrome and cause of death in cancer patients but its pathogenesis is still a matter of controversy [1]. The syndrome is observed in a wide variety of tumours, so to understand it one approach would be to look for what they share, like growth, rather than their differences. What are the metabolic characteristics of an actively growing cell? What is the physiological response of the organism to a local growth demand? Is that response normal or pathological?

The particular demands of a tumour depend on the fraction of cells growing and their growth rate [2]. The tumour cells have an enzymatic phenotype similar to that of embryos [3]; both are growing populations. The tumour cell population has to be viewed within the cell community that constitutes the organism. In this context there are several points that are needed to understand the metabolic interaction of different cell populations:

Existence of individual metabolic phenotypes, e.g., growth.

Existence of localization of specific functions that are performed by an organ for the benefit of the whole organism, e.g., gluconeogenesis in liver.

Cells are continuously fed from the organism stores. Stores are replenished in a non-continuous fashion by exogenous ingestion.

The flow of nutrients between different pools of the organism, separated by membranes, is affected by concentrations and ratios of nutrients at both sides of the membranes.

2. AMINO ACID POOLS

In order to study the effect of tumourigenesis on amino acid metabolism we must first determine what different compartments are involved. There are two types of amino acid pools: a fast reacting pool formed by free amino acids of intracellular and extracellular locations, their main reservoir being the muscle. The second type, a slow reacting pool, is formed by proteins, which is mainly an intracellular pool with skeletal muscle as its main component. The interconversion between the two pools takes place intracellularly [4]. The fast reacting pool is characterized by its high mobility and changes due to the exogenous supply by diet or utilization by individual groups of cells. Between the muscle reservoir and the rest of intracellular individual pools is the plasma pool, small in size but at the center of all daily fluctuations in the

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organism, working as a bridge pool among different cell populations. A diagram of these pools and the flux among them in a cancer patient is shown in fig.1. For growing cells there is a one-way flux since the cells are taking up amino acids; in contrast the reservoir organ, muscle, has a two-way flux, storage and maintenance of supply to other cells, so there is a localization of storage and utilization of amino acids.

Between these different free pools there is a membrane barrier with several transport systems each of them involved in the translocation of a particular group of amino acids; these transport systems can operate in both directions and have particular properties [5,6] but their function in the presence of several amino acids using the same carrier system from both sides of the membrane is not yet known. So far transport regulation is poorly understood in this context, but is of vital importance for the understanding of interorgan nutrition [5].

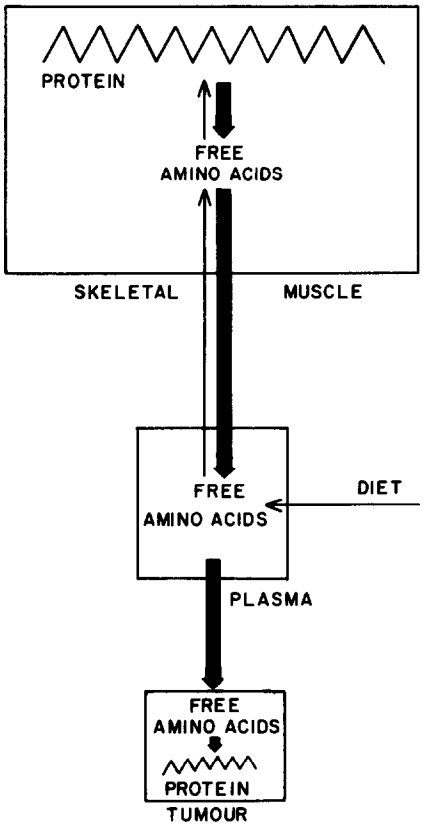

Fig.1. Flux of essential amino acids among different pools in an adult cancer patient.

3. TUMOUR EFFECTS ON AMINO ACID METABOLISM

The growing tumour is making a demand on nutrients required, e.g., essential amino acids. The tumour growth will deplete its essential intracellular amino acid pool, unless there is an extracellular source (plasma) but for growth it is important to keep the internal amino acid concentration at an adequate level, so the free intracellular pool connected with the extracellular one creates a downward gradient towards the inside of the tumoural cell (fig.1); it is important to note that the transport system for leucine works better in that way [5]. The plasma pool can be depleted in a short time because of its small size, a 300 g tumour can do it in less than 1 day, but before this happens the muscle free amino acid pool will respond to the extracellular changes no matter what the origin of the demand, since the muscle does not discriminate but just senses a demand. This response would be a release of amino acids from the muscle free intracellular pool and this would be reflected in muscle metabolism, first as a decrease in its ability to synthesize protein [7,8], resulting in net loss without increasing degradation, at later stages degradation will also increase [19]. This reaction might initially be observed as a negative nitrogen balance. Muscle studies in patients confirm these predictions [7,8]. The demand for essential amino acids has been observed in cancer patients [9]. But while essential amino acids have a destination, non-essential amino acids mobilized at the same time contribute to the host metabolic picture, e.g., altered amino acid ratios, negative nitrogen balance and satiety [10].

4. LEUCINE STARVATION

Leucine is probably the most studied amino acid in tumours. We can make a model situation by studying the effect of the tumour needs on the daily leucine requirement [11]. As a tumour value, I have used 30 nmol/min per g cells, based on the total utilization of leucine [12]. This value correlates well with individual aspects of leucine metabolism studied in patients [9]. The tumour can increase considerably the daily need of leucine (fig.2). This increase has a better correlation with the clinical deterioration of the patient [2] than the

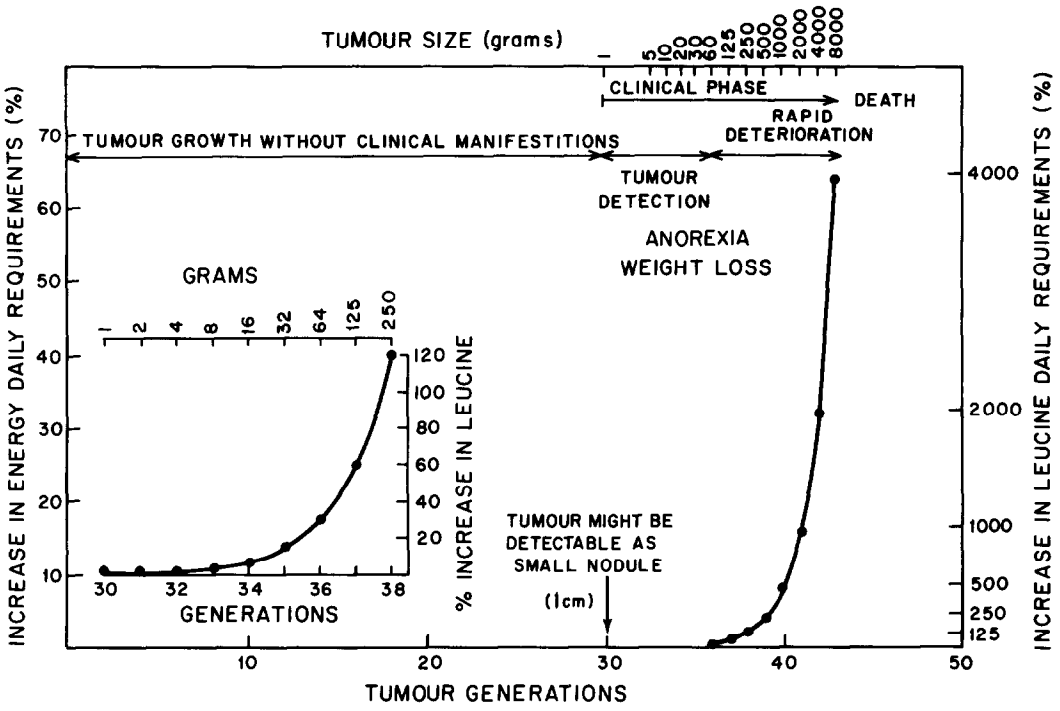

Fig.2. Effect of tumour growth on the daily requirements for energy and leucine recommended by FAO/WHO [11] for a standard individual. Inset shows expanded the beginning of the clinical phase. The rates for glucose utilization and lactate production as well as overall leucine utilization are based on data from experimental animal [12]. Tumour size represents that of the actively growing population, that is likely to be a fraction of the total tumour population.

modification of carbohydrate and energy metabolism. Other essential amino acids are likely to follow a similar pattern but no study is available either in humans or experimental animals. This demand will create an amino acid flux towards the tumour.

5. AMINO ACID METABOLISM IN CANCER PATIENTS

The study of several parameters of protein metabolism in cancer patients shows a 33% increase in whole-body protein turnover with respect to non-cancer patients and starved non-cancer subjects [13]. The most striking feature is that the ratio of protein catabolism to protein synthesis is the same in both groups (fig.3) and independent of the nitrogen balance, suggesting that the coordinated regulation of both processes is maintained in the cancer patients [14]. This observation is consistent with the amino acid pool response where regulation is indispensable.

Similar alterations of protein metabolism have been reported in other situations, e.g., healing after surgery and trauma [15–17]. In all of them there is a locally growing cell population sug-

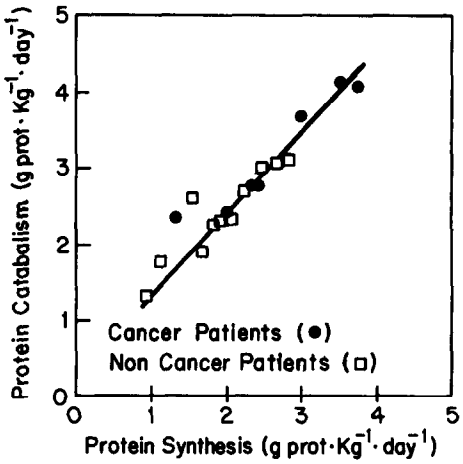

Fig.3. Correlation between protein catabolism and protein synthesis in cancer and non-cancer patients [13].

gesting that the metabolic alteration is more likely to be the organism response to a local demand than tumour specific. If there is a growing cell population competing for nutrients with the tumour, cachexia will not be observed. This is the case of tumours in children [18].

6. CONCLUSION

Cachexia is the extreme manifestation of the host metabolic adaptation to local tumour growth and consequently common to most malignant tumours. The tumour has a heavy demand for essential amino acids from the beginning of its clinical phase and the different amino acids pools and their regulation are the basis of the host response. In this metabolic picture the individuality of each tumour will add the variability aspect that might distort the metabolic host response to local growth. The host response, insofar as it can cope with the tumour demand, is a physiological reaction.

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