Hypothesis

TUMOUR INDUCTION OF HOST LEUCINE STARVATION

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1. Introduction

Cachexia, the main cause of death in cancer patients, is a terminal metabolic condition which starts with a negative nitrogen balance and weight loss and continues until it reaches its final characteristic clinical picture. This process is usually quite fast in development. This progressive condition is likely to be the result of the metabolic interaction between the tumour and its host, an area that has generally received little attention compared with other aspects of tumour–host interactions. In order to understand this metabolic tumour–host interaction, we need to know the tumour requirements both for energy and for essential nutrients. Data has become available for a mammalian cell, a line of ascites carcinoma [1]. I have applied these data in a model situation. The tumour requirements for energy and leucine are examined in the light of the daily exogenous requirements of the host, estimated by the requirements of the average man as reported by FAO/WHO [2]. I reach the conclusion that a fast growing tumour increases significantly the leucine requirements of the host, without having an effect on the energy needs.

2. Effect on energy requirements

Malignant tumours are heavily dependent on the anaerobic utilization of glucose under aerobic conditions, aerobic glycolysis, as the main energy source [3]. The more malignant the tumour is, the more dependent it is on aerobic glycolysis [3]. Ascites cells, a highly malignant tumour, use glucose at 2 μmol . min^{-1} . g $cells^{-1}$; 90% of this glucose is converted into lactate and provides 80% of the total energy production by the tumour [1], the remaining coming from glutamine oxidation. If the lactate is reconverted into glucose by the host liver, it would represent an expenditure of 2 mol ATP . mol recycled $glucose^{-1}$, and the tumour would be acting as an ATPase. This extra expenditure of energy represents a $<0.5\%$ increase in the daily energy requirement of the host, 2500 kcal . day^{-1} [2], even if the tumour size is 200 g (fig.1). The alternative possibility, that lactate is oxidised peripherally by the host, would represent only a slightly less efficient use of carbohydrates, but still would account for $<1\%$ of the daily energy supply. Probably in the host, lactate follows both fates. These data suggest that the tumour, even if it is a fast growing one, is not an energy drain on the host in a direct way, that is, as a consequence of the tumour needs.

3. Effect on leucine requirement

The effect of the tumour on the organism's leucine requirement can be seen by reference to its effect on the daily intake of leucine for the host. The recommended daily intake is 1.1 g leucine . day^{-1} [2]. That recommended level is twice the actual need, though the leucine used by the tumour is of both exogenous and endogenous origin. In fig.1, we can see that there is a very significant increase in the exogenous intake of leucine as tumour size increases. The rate of leucine utilization by the tumour is 30 nmol . min^{-1} . g $cells^{-1}$ [1]; this value is the net incorporation of leucine into proteins and lipids once a balance between synthesis and degradation has been achieved. It represents the use of leucine by a heterogeneous population of tumour cells, as they are in the animal. This rate makes the tumour a drain on the leucine sources, and the consequent deprivation for the host of an essential amino acid leads to the waste of other amino acids and to the net loss of less-vital proteins in the organism, either by stopping their synthesis or by

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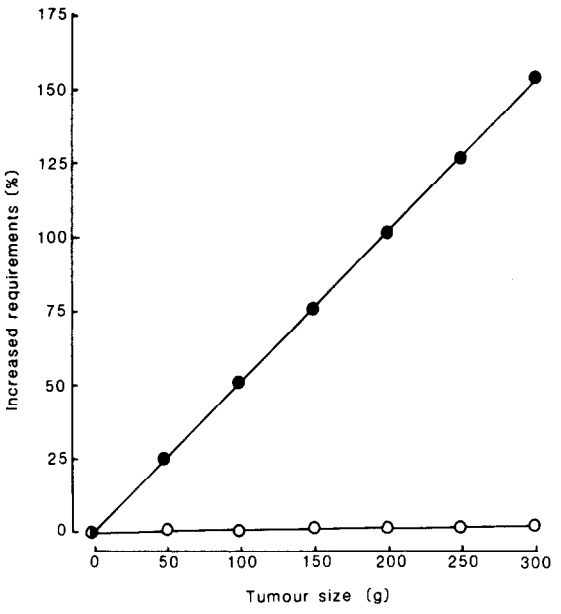

Fig.1. Effect of tumour on the daily intake of leucine (•) and energy (o). The reference values are the recommended daily intake of the host in the absence of tumour, according to FAO/WHO [2]. For the energy calculations, it is assumed that lactate produced by tumour cells is recycled by the host's liver. One gram of cells is equivalent to ~3.5 X 10^9 cells.

degradation as a compensatory effect. In experimental tumour bearing animals, a net uptake of essential amino acids has been observed by measuring the arterio–venous difference in amino acid concentration in the hind leg bearing the tumour, but no correlation with tumour size, number of cells or rate of growth was made [4].

Two groups [5,6] have observed that in tumour bearing animals there was a significant decrease in the rate of protein synthesis in muscle. There was also a slightly increased rate of protein synthesis in liver, probably as a result of this organ's role in general homeostasis, which may increase the demands made on other tissues to supply amino acids. A drop in protein synthesis in muscle is also observed as a result of protein starvation [7]. The mechanism by which a decrease in protein synthesis is induced in peripheral tissues, mainly muscle, as a result of dietary manipulations or by increased overall requirements due to the tumour seems to be the consequence of essential amino acid deprivation leading to uncharged tRNA [8]. Nevertheless, during the initial stages of the tumour, this drainage can be easily overshadowed by several factors like age, sex, physical activity, weight, quantity and quality of the diet and perhaps the timing of food intake, efficiency of nutrient utilization and other particular tumour effects, though the effects of these factors may be very variable. Despite all these factors, a recent and very carefully controlled clinical study [9] clearly points to a problem of protein starvation rather than an energy one in cancer patients.

4. Amino acid pools and the preferential use of leucine

One question that stands out is, why does the tumour not suffer a drop in the rate of protein synthesis if it is the subject of the same regulatory mechanisms as normal cells [8]. This focuses the problem on the preferential use of nutrients by a particular group of cells. The metabolic conditions in a tumour may be similar to those in normal situations in which there is a group of cells under rapid proliferation, for example pregnancy [10], and the healing period after surgery [11,12]. In both cases, a negative nitrogen balance can easily be achieved. In tumours, there is a switch to a foetal isoenzyme pattern; this may be partly responsible for the appearance in tumour tissues of metabolic characteristics similar to those in the embryo [13].

The selective use of nutrients can be the result of the characteristics of different amino acid pools in the organism and the interactions of these pools. Tumours and other fast growing cells are characterized by having a very small free leucine pool, and by having a very high utilization of this pool by each unit of mass of cells, in such a way that its use results in a net loss of leucine in the organism. This loss occurs either by incorporation of the leucine in lipids or in proteins. Despite the fact that the protein is a mobile pool, in practical terms of leucine availability to the host, this incorporation can be regarded as a net loss, consequent on the growth of the tumour. Because of this net loss, the intracellular pool is depleted. This creates within the cell a net flux towards protein/lipids, and if no exogenous supply is made available, this flux would lead to a sharp fall in the intracellular concentration of the amino acid. However, the free intracellular amino acid pool is in contact with the pool in plasma, which is also small, and as a consequence of this contact, a concentration gradient is generated towards the inside of the cell. This might help the

active transport system, resulting in a net uptake [4] of the amino acid by the cell. From the data given in fig.1, we can see that a 100 g tumour would completely deplete the plasma of leucine in ~15 h. The plasma level can be maintained either from the exogenous supply from the diet, or from muscle. More than 50% of the total free amino acid pool of the organism is contained in muscle, with an intracellular concentration higher than that in plasma. The use of the muscle amino acid pool per unit of mass is very low [14]. The consequence of this is that muscle comprises a large reservoir that can be mobilized by the demands of other groups of cells that have an effect on the plasma levels. Thus, we have a situation in which the equilibrium between the muscle and plasma pools can be altered, generating a net flux of leucine towards the plasma. This net outward flux of the amino acid from muscle has been observed during daily periods of fasting in man [14]. It is highly likely that it also occurs in a case such as this, where there is an increased demand for nutrients due to the tumour requirements. We must remember that leucine is carried by the system L of amino acid transport which operates very well in an outward direction [15,16], and furthermore is able to carry most of the essential amino acids.

We can summarize the situation by saying that a concentration gradient between the free amino acid pools is created with a net flux towards the cell which is causing a net loss of leucine (muscle → plasma → tumour cell). This is a simplified explanation that can account for the phenomena of negative nitrogen balance, wasting of muscle, and weight loss observed. However, elucidation of the mechanism accounting for these phenomena, if correct, will have to await a better understanding of the regulation of amino acid pools and their interactions, of the regulation of active transport systems by modification of amino acid concentrations, and of the amino acid ratios on either side of the cell membrane.

5. Conclusion

A tumour characterized by rapid growth increases significantly the host requirement for leucine, while having no effect on the overall energy requirement. This situation may be one of the factors responsible for cachexia in cancer patients and can be explained as a result of the interaction between different amino acid pools in the tumour bearing animal. A better knowledge of the metabolic interaction between a tumour and its host will be possible when data for the requirements of human tumours become available, and as these requirements are examined within the framework of the tumour–host relationship, both theoretically and experimentally. This knowledge, when available, may be of use in the management of cancer patients.

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