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Review

Arginine deprivation and metabolomics: Important aspects of intermediary metabolism in relation to the differential sensitivity of normal and tumour cells

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Abstract

Arginine deprivation causes many types of tumour cells to die, often because they cannot recover or convert urea cycle intermediates into arginine. The powerful homeostatic mechanisms that kicks in to restore arginine levels in vivo are lacking in vitro, where there is no supply of citrulline. Comparison between cells deprived of arginine by direct elimination methods or indirectly via arginine degrading enzymes should show differences depending on their ability to handle alternative intermediates (ornithine, citrulline and argininosuccinate) of the urea cycle. The internal state of cells that *can*, versus those that *cannot*, use intermediates will metabolically be quite different. These differences should provide clear indicators regarding the sensitivity (susceptibility) of cells to arginine deprivation, from which we will be in a much better position to judge which tumours to treat, and possibly how to design the best treatment to eliminate them.

Keywords: Cancer; Arginine; Arginase; Citrulline; Ornithine; Deprivation; Catabolism; Cell proliferation; Cell death; Channelling; Urea cycle intermediates; Argininosuccinate synthetase; Argininosuccinate lyase

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1. Introduction

After more than 50 years of knowing that arginine deprivation can act adversely on tumours, for example see [1], the possibility of this becoming an accepted cancer therapy has only more recently begun to be explored in earnest. In general, the evidence indicates that the original concept was probably sound, but the details and "technology" required to achieve a therapeutic state demanded considerably greater insight and have needed much more development work than originally envisaged (the bulk of which has not been published, for obvious reasons). Also, we were relatively ignorant of the spectrum of activities in which arginine was intimately involved. The possibility that the emerging art of metabolomics will provide a valuable tool clearly raises an interesting question that will be examined and discussed in this report. However, there is a large caveat. The constellation of small molecules as opposed to nucleic acids and proteins inside cells arrive there through different portals and via different nutritional and physiological processes. If we knew more about how they got there, why they have accumulated to detectable levels, and more about the flux of each of them (and there may be many thousands that we ought to be considering), then we need some insight to make the most of this information, although the "signatures" at any moment in time may themselves "suggest" a particular cellular status or functional role. The relationship between cause (of the metabolomic profile) and effect is extremely tenuous, and perhaps so trivial as to be close to totally meaningless most of the time. The cell is truly dynamic, and a "snap-shot" of its metabolome can hardly expect to capture what is the true state of the cell as a dynamic entity that exists in four dimensions. If we are to believe the quite marked oscillations that occur in biosynthetic functions, even protein synthesis [2], we see also the shortcomings of a snap-shot taken at any point on such a curve.

Yet despite these towering, almost intimidating, problems, there are many who have faith in the belief that the "general complexion" of the metabolic profile can really tells us something. This is akin to body language. If I am sweating and pale, this will signal something quite different from when I am sweating and red. If the metabolome shows a high cholesterol content and a low tyrosine content, will that tell you anything more than if it has a low cholesterol and a high tyrosine content? General metabolomic profiling may not be of much use (provide little information), whereas homing in on specific pathways within the whole constellation might have significant benefit. Perhaps this will be the case when we look at differences between cells under two radically different regimes, i.e. replete with arginine and devoid of it. But I cannot stress enough that if we know so little about intracellular "pools", how is it we can make use of general intracellular concentrations of, for example, overall amino acids levels at any instants? A lifetime's work has brought us only a little understanding of a few intracellular pools [3,4]; it will take infinitely longer before we can understand the composition, locations and interactions of thousand of pools that must simultaneously be present in the cell.

2. Arginine deprivation: proof of principle

In establishing beyond doubt that arginine deficiency is tolerated very poorly by certain types of tumour cells, the bulk of the initial work involved in vitro studies that confirmed the notion that deprivation offered a "rational" strategy [5]. Subsequently, some fascinating work began on tumour models in animals, and latterly there have been trials on terminal (named) patients [6–8]. While these latter reports are the very first to come through on human patients, it has to be appreciated that these have taken place only within the last couple of years, and therefore, it may be some time before sufficient clinical work has been done to establish that arginine deprivation will be adopted as an anticancer strategy on its own, or more probably in combination with other modalities. The actual amount of work done on animal tumours has been relatively little. The situation both in vitro and in vivo has been largely summarised in our reviews [9–11]. Thus, this article will consider the main tasks that are now in hand, which are primarily concerned with: (i) continuing refinements that are needed in the application of arginine deprivation as a potential strategy in cancer therapy to as wide a spectrum of tumours as possible, (ii) the types of tumours upon which it is likely to be most effective employed, down to the individual sensitivities of tumours within any type, (iii) the question of whether the metabolome of cells provides valuable and useful data in diagnosis and prognosis, and also in monitoring the progress of treatment. Without doubt, metabolomics is relevant and could be useful in characterising tumours and patients in future, but this art is too young to decide before more data is collected where its real strength lies. In addition, data can quickly be gleaned that might be of some empirical and immediate value if responses to therapy correlate well with the profile of intermediate of metabolism at any particular time. However, if we are to understand what the patterns means so that more rational applications (customisation) of arginine deprivation can be devised, clearly metabolomics will help in certain protocols in cancer therapy, but its scope here will remain sharply focused on arginine deprivation. Indeed, the fact that we are dealing with a substrate and a substance that enters a multiplicity of complex metabolic pathways (Fig. 1), and are concerned with what happens when it is removed from the system, makes sense in terms of being analysed by a metabolomics approach—it is almost as if arginine deprivation provides an "acid test" of metabolomics in cancer treatment.

3. Basic information about the arginine requirements of living systems

Let us first consider some of the basic "facts" about how arginine deprivation came to be considered a potentially