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Increased cell hydration promotes both tumor growth and metastasis: A biochemical mechanism consistent with genetic signatures

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Summary It was postulated previously that a progressive increase in cell hydration, induced by successive genetic or epigenetic changes, is the basic mechanism of multistep carcinogenesis, and also that the degree of malignancy increases with the degree of cell hydration. These hypotheses implied that increased cell hydration is a common factor promoting both tumor growth and metastasis, and that metastatic potential increases with the degree of cell hydration. This paper discusses these implications in relation to current concepts of genetic mechanisms determining the acquisition of metastatic potential. It was also postulated previously that the enhancement of metabolic activity by increased cell hydration will increase the ability of tumor cells to compete for nutrients with their normal counterparts. This effect may favor the preferential selection of cells whose genotypes confer the greatest increase in cell hydration and which, on the present hypothesis, would be those with the greatest capacity for metastasis. An important feature of this ''common factor'' hypothesis is that it suggests a *biochemical* explanation for DNA-microarray data showing a similarity between the gene expression patterns associated with both tumor growth and metastasis, while the postulated role of genes causing increased cell hydration might explain the apparent acquisition of metastatic potential at an early stage of tumorigenesis. Previous investigations were consistent with the hypothesis that various factors promoting carcinogenesis may do so by increasing cell hydration. A survey of the literature showed that all of these factors also promote cell motility, migration or metastasis, and provided evidence that these effects could be attributed to the associated increase in cell hydration. Methods are suggested for testing the hypothesis, and the paper concludes by emphasizing the need for more research on the biochemistry of cancer, and on the role of water as a biochemical factor of particular importance, not only in carcinogenesis, but in many other aspects of cell biology.

Introduction

In a previous paper on the role of cell hydration as the primary factor in carcinogenesis [1] it was postulated that a progressive increase in cell hydration, mediated by successive genetic or epigenetic changes, is the basic mechanism of multistep carcinogenesis. It was also postulated that the degree of malignancy increases with the degree of cell hydration. Since the capacity to metastasize is the most characteristic feature of malignancy,

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these two hypotheses implied that increased cell hydration is a common factor promoting both tumor growth and metastasis, and also that the metastatic potential of tumor cells increases with their degree of cell hydration. This paper presents evidence consistent with these implications and suggests methods for testing their validity.

Background

The acquisition of metastatic potential, the major cause of cancer mortality, has been the subject of numerous investigations, yet there is still considerable uncertainty about the nature of the mechanism involved. Two of the more recent papers on this subject are of particular relevance to the present hypothesis. In one of these Bernards and Weinberg [2] questioned the validity of the concept that the acquisition of metastatic potential is determined by specific genes expressed at a late stage of tumor development [3,4]. They suggested that a metastatic phenotype would be unable to promote the increased cell proliferation required to compensate for the infrequency with which the multistage process of metastasis is successfully completed. As an alternative hypothesis, they proposed that genetic changes promoting cell proliferation and tumor growth e.g. expression of such oncogenes as *ras* and *myc*, perhaps combined with the inactivation of certain tumor suppressor genes, may contribute to the proclivity of tumors to metastasize later in tumorigenesis. In a further discussion of this concept, Gupta et al. [5] suggested that the genetic promotion of cell proliferation and tumor growth may provide the opportunity for the occurrence of additional genetic changes that may favor the acquisition of metastasis. The concepts proposed in both of the above papers are consistent with my ''common factor'' hypothesis, which implies that selection of genes causing increased cell hydration, and the consequent stimulation of cell proliferation, will promote both tumor growth and metastasis.

It was also proposed previously [1] that increased cell hydration, in both plants and animals, enhances the general level of metabolic activity (see references cited), an effect that may be expected to include acceleration of the aerobic respiration characteristic of the initial stage of carcinogenesis, and also of the glycolysis that becomes an increasing source of energy during subsequent tumor development [6]. It was suggested that this effect may increase the ability of tumor cells to compete for nutrients with their normal counterparts, and may thus play a major role in the mechanism of multistep carcinogenesis. It may also favor the preferential selection of cells whose genotypes cause the greatest increase in cell hydration, and which, on the present hypothesis, would be those with the greatest metastatic potential.

An important aspect of the present hypothesis is that it could provide a *biochemical* explanation for data obtained by DNA-microarray analysis. For example, it might account for the close similarity between the pattern of gene expression of cells from both primary and metastatic tumors [7,8]. It is also consistent with evidence that metastatic potential may be acquired at an early stage of tumor development [7,9]. Theoretically, this evidence, which would seem to be at variance with the usual process of Darwinian selection, might be attributed, on the present hypothesis, to the early expression of oncogenes such as *ras and/or myc*, both of which cause large increases in cell hydration (see references cited in [1]). Another mechanism that might promote the early acquisition of metastasis is suggested by the frequent occurrence of fetal proteins in tumors [10], a feature consistent with the concept that cancer may be regarded as a progressive reversal to an embryonic condition [1]. Expression of these fetal genes might promote the increased cell hydration which is characteristic of both tumors and embryos, thereby reducing or eliminating the need for additional genetic changes to induce the acquisition of metastasis. This suggestion agrees with the hypothesis that the cell type of origin may play a significant role in the genetic mechanism promoting the occurrence of metastasis [5].

Correlations between cell hydration, carcinogenesis and metastasis

Previous investigations provided evidence that various factors promoting carcinogenesis may do so by increasing cell hydration [1]. These carcinogenic factors were: (a) oncogenes e.g. *ras, myc* and *Akt;* (b) inflammation e.g. the edema induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA); and hormones e.g. insulin and estrogen. A survey of the literature showed that all of these factors also promote the induction of cell motility, migration or metastasis. The hypothesis that these effects are causally related to the associated increase in cell hydration is supported by several investigations showing that factors affecting cell hydration play a major role in the regulation of cell motility and

migration, essential prerequisites for the acquisition of metastasis. Studies on neutrophil migration showed that both cell volume and migration were inversely correlated with the osmolarity of the extracellular solution to which they had been exposed [11]. Their migration was also dependent on water influx, which was postulated to promote generation of the cell protrusions required for lamellipodia formation and cell locomotion, and attributed to expression of Aquaporin-9, a gene which increases cell membrane permeability to water [12]. A similar mechanism was postulated to play a major role in the promotion of cell migration in mice by Aquaporin-1, an effect which was greatly reduced by Aquaporin deficiency [13]. Besides these physical effects, increased cell water content, as mentioned above, may enhance metabolic activity, including respiration and glycolysis, thereby providing the additional energy required for cell motility[14]. One might speculate that the amount of this additional energy could influence the degree of metastatic potential.

Testing the hypothesis

Measurements could be conducted to test the implication of the present hypothesis that the water content of malignant tumors is higher than that of benign tumors. However, any such difference may be reduced by the occurrence within the benign tumors of clones possessing varying degrees of malignancy. If confirmed, the higher water content of malignant tumors would suggest, in agreement with the present hypothesis, that the degree of cell hydration sufficient to promote increased cell proliferation, as in benign tumors, is less than that required to induce metastasis. The additional hypothesis, that the degree of malignancy i.e. metastatic potential, increases with the degree of cell hydration, could be tested by examining the correlation between the volume of cells isolated from malignant tumors and differences in their metastatic potential. Samples from the well-defined and readily accessible stages of colorectal tumorigenesis, a system frequently used in studies on multistep carcinogenesis [15] may also provide suitable material for such comparisons.

Clinical implications

It was suggested previously that the Achilles' heel of the cancer cell may be its increased sensitivity to desiccation, and that this might be exploited therapeutically by treatments which reduce the degree of cell hydration [1]. The present hypothesis suggests that the effectiveness of such treatments may be enhanced by their ability to inhibit both tumor growth and metastasis.

Concluding comments

The recent introduction of the technique of DNA-microarray analysis has greatly increased our knowledge of the genes that play a role in both the promotion and prevention of cancer. However, as previously suggested [1], the potential value of the vast amount of data from genetic investigations is limited by an insufficient understanding of the biochemical mechanisms that mediate genetic effects at the cellular level. It is hoped that this paper, together with the previous one [1], will promote a greater interest in the role of water as a biochemical factor of particular importance, not only in the mechanism of carcinogenesis, but in many other aspects of cell biology [16].

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