

Epigenetic Carcinogenesis and Malignancy: The Significance of Migratory Potential

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Abstract: The essential feature of the malignant phenotype is the ability of the affected cells to transgress the normal territorial limits that delineate tissue boundaries. This brief review outlines the process underlying the acquisition of this property based on evidence consistent with the notion that the mechanism of carcinogenesis involves defective epigenetic transmission. The resulting failure of vertical transmission of the differentiated pattern of gene expression in proliferative stem cells which leads to faulty copying of the epigenetic information at each cell division generates widespread genetic abnormalities; a process which is essentially equivalent to a greatly elevated mutation rate. The outcome from the point of view of the affected cell and its progeny would be expected to interfere negatively with the proliferation rate. To some extent this proliferative disadvantage is offset by the altruistic factor necessary for permitting coexistence of different cell types in multicellular organisms but the crucial property which renders certain cells malignant is their ability to transgress tissue boundaries. Affected cells possessing this malignant phenotype are able to penetrate this barrier and enter microenvironmental zones where they are able to proliferate without competition. The competitive growth process is outlined using a simple microenvironmental model.

Keywords: Logistic growth model, cellular altruism, migratory limitation, malignant phenotype, penetration of tissue barriers, epigenetic error, faulty epigenetic copying at mitosis, metastasis.

INTRODUCTION

In previous publications the evidence consistent with the proposal that malignancy arises from acquired defects in the epigenetic copying process is set out [1-3]. The process results in the production of cells exhibiting multiple genetic abnormalities. Many of the structural and functional abnormalities have the effect of diminishing the proliferative efficiency of the affected cells but this growth disadvantage is offset by the acquisition of the property of anomalous transmigration. The significance of abnormal migratory potential in the expression of malignant characteristics is here discussed in relation to an *in silico* model of population growth.

DOMAIN MODEL

One of the most remarkable features of evolutionary biology is the emergence of organisms composed of cooperative assemblies of cells expressing different metabolic features. These multicellular organisms, derived from a single progenitor cell, undergo a process of proliferation and differentiation that involves the activation of certain genes and the silencing of others which is the result of a set of mechanisms known as epigenetics. However, since the survival of the cells is determined by Darwinian proliferative competition, the process is dependent on a mechanism which enables the survival of subsets of cells that are

by virtue of their differences in gene expression less proliferatively competitive. In other words there is a fundamental requirement for proliferative altruism. This situation can be illustrated by a simplified two-dimensional model in which an environment is envisaged in which cells are able to grow. The limit of growth is determined by the availability of nutrients and the loss of waste materials so that the total occupancy is given by a logistic constant.

Using this approach, the maximum number of cells per domain is limited by the logistic parameter K and the growth equation for population A is described by:

$$\frac{dA}{dt} = rA \left(1 - \frac{A}{K} \right) - \lambda A$$

Where r represents the proliferation rate, and λ the loss rate.

In order to take account of more than one cell type, competitive exclusion is prevented by cellular altruism (α), so that the growth equations for populations A and B are given by:

$$\frac{dA}{dt} = r_1 A \left(1 - \frac{\{\alpha_1 A + B\}}{K} \right) - \lambda_1 A - m_1 A$$

$$\frac{dB}{dt} = r_2 B \left(1 - \frac{\{A + \alpha_2 B\}}{K} \right) - \lambda_2 B - m_2 B$$

Cellular exchanges between adjacent domains are dependent on the migratory ability (m). If there are no

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barriers to migration the diffusional exchange between the adjacent six domains is determined by the sum of the relative density, e.g.:

$$mA = \mu \sum_0^n A - A$$

In the presence of a barrier to migration $\mu=0$ so that no migration takes place.

Employing this simplified model of cellular proliferation it is possible to show that a class of cells with diminished growth rate is able to thrive by virtue of their insensitivity to the migratory barrier which enables them to enter territory where there is no proliferative competition. This is illustrated in Figure 1.

The competitive growth model represented in this illustration consists of two cell populations viewed in

adjacent growth domains with limited resource availability. The size of the population in each circular domain is indicated by the radius of the circles.

The normal population A is indicated in black and the cells occupy a central region consisting of 37 domains. In the initial state of the model each of these domains is occupied by a steady-state number of cells which are able to move freely between these domains but are prevented from migration beyond the margin of the normal occupancy. The model begins with the emergence of a second population B, shown in red, starting with a single mutant cell in the normal domain (third from the left on the bottom row). The proliferative parameters of the two cell types are very similar, as shown in Table 1 below, but the illustration shows the development of the competitive growth pattern resulting from the ability of the red population to migrate into unoccupied domains surrounding the black region.

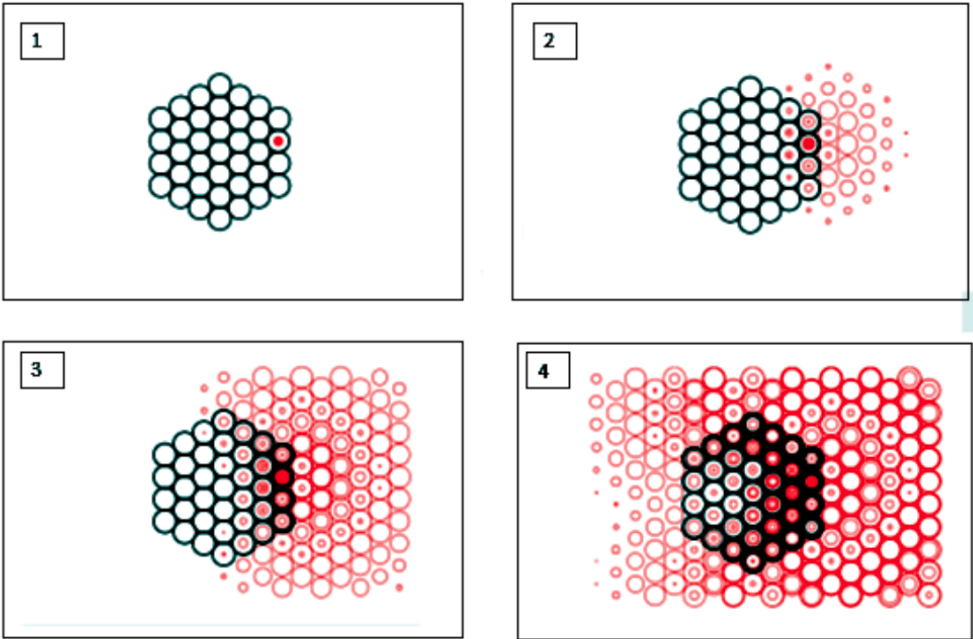


Figure 1: Competitive Growth Model. Panel 1 shows a hexagonal array of cells (population A) outlined in black in which a mutant population B (shown in red) has arisen which is able to migrate into domains both inside but also outside the normal array.

Table 1: Comparison of Proliferative Parameters of Competing Populations

	Population A (black circles)	Population B (red circles)
Proliferation rate	0.02	0.015
Loss rate	0.001	0.001
Altruistic constant	1.1	1.1
Migration rate	0.001	0.001
Resource requirement	1	1
Barrier sensitivity	1	0

In the normal region the gradual growth of the red population results in the erosion of the black cells and in this zone these competitive populations coexist as a result of the altruistic properties they each exhibit. However, the ability of the red cells to penetrate the migratory barrier and proliferate in the surrounding uncontested domains gives them the overall growth advantage despite their marginally lower proliferation rate. This illustrates the fundamental model of malignancy.

DISCUSSION

As indicated by the application of the domain model illustrated above it is possible to explain the emergence of malignancy on the basis of epigenetic error if the faulty vertical transmission of gene silencing affects the migratory properties of the affected cells such that they acquire the ability to transgress the normal tissue boundaries. This provides conditions that enable entry into zones where there is diminished proliferative competition and enables the selected subclones to metastasize widely. At present there remain problems regarding the nature of tissue barriers and the functional processes that are involved in their penetration, but these processes are controlled during embryogenesis so that they are normally regulated by mechanisms implicated in differentiation.

The Nature of the Migration Barrier

Whilst this model provides a satisfactory explanation of the proliferative behaviour of malignant cell variant cells the mechanistic details of the migration barrier and the processes that lead to the ability of malignant cells to lack sensitivity to the barrier conditions are far from clear. It has been proposed that the acquisition of abnormal transmigratory behaviour in adult cells is the result of epigenetic error leading to the re-expression of migratory genes that are normally active during embryogenesis. In the fully developed organism the retention of proper functionality is dependent of the limitation of migration, and barriers to migration must reside in the failure to permit the formation of adequate adhesive interactions between the locomotory apparatus of the cell and the extracellular environment. The nature of the domain boundaries has been discussed in relation to proteoglycans. There is much evidence that motility involves divalent cation binding and barrier tissues contain proteoglycans that act as potent modifiers of cell adhesion [4-17]. Thus the pattern of restriction of cellular migration may be controlled by genes generating proteoglycans or proteoglycan-degrading

enzymes [18, 19]. On the other hand, there are problems with the notion of barrier generation since the essence of the malignant potential rests with the invading cells which argues that it is a feature intrinsic to cancer cells and may therefore represent a functional aspect of cellular motility. One conceivable possibility is differential sensitivity to the local calcium ion concentration [19]. Such a feature would permit some classes of cells to migrate in localities where others are immobilised, as in the example given herein. For example, cells overexpressing L-type calcium channels may possess a migratory advantage and there is evidence that cancer cells manifest high levels of these voltage-gated calcium channels [20].

CONCLUSION

The model illustrated in this brief outline enables the generation of malignant behaviour to be explained in terms of defective epigenetic control.

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CONFLICT OF INTEREST

There are no matters discussed that raise any question of conflict of interest.

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