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PERSPECTIVE

Cellular Proliferative Domains: Barriers to Migration

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Abstract

An important aspect of the analysis of the proliferation of cell populations as composed of a set of intercommunicating logistic domains is the nature of the barriers between adjacent domains and the regulation of cellular migration between them. The nature of these inter-domain boundaries is discussed in relation to the central role of L-type calcium channels in the control of cell motility and it is proposed that domain boundaries are determined by proteoglycans which act as calcium chelators and hence regulate the local extracellular Ca^{++} concentration. The selective migratory advantage gained by overexpression of calcium channels is briefly alluded to.

Introduction

A possible analytical approach to modelling the growth of cell populations is to consider the microenvironment in which they exist as composed of a set of adjacent autonomous virtual domains logistically limited by the local nutrient supply and other essential resources [1]. For simplicity, each domain is regarded as spatially defined and of equal size. Transfers of cells between domains take place by migration and are treated as a diffusion process that reflects the relative cell density in adjacent domains. To take account of considerations of tissue architecture it is proposed that there are defined barriers to migration that limit the extent to which cells are able to move between domains. In this brief communication the possibility that these barriers might consist of proteoglycans is explored in connection with their possible interference with cell migration.

The Significance of Calcium Ions in Cell Motility

In order to migrate cells need to adhere to the extracellular matrix by localised traction points through which mechanical force exerted by cytoskeletal elements can bring about movement. This process is dependent on integrins, a set of transmembrane proteins that are able to form adhesions to matrix components [2]. Integrins are present on the cell surface and, when activated, are able to form adhesions with extracellular matrix components. Adherent integrins have been shown to activate L-type calcium channels [3,4] and the localised calcium entry into cells acts as an activator of several processes that are involved in the establishment and turnover of focal adhesions through which cell motility is brought about. In particular there are several processes that are calcium ion dependent including activation of the intracellular protease calpain-1 [5] which is implicated in the stabilisation of filopodia [3] and also in the turnover of focal adhesions which is essential to permit directional movement [6,7]. Also, the focal adhesion kinase, which is instrumental in producing myosin contraction of the cytoskeleton, is calcium-dependent, possibly through the activating phosphorylation pathway [8]. It appears that these events are controlled by waves of localised calcium ion entry [9,10] brought about by L-type calcium channels. L-type calcium channels are formed from multiple subunits of which the α1 subunit acting as the central transporter core that enables Ca^{++} to enter the cell through the plasma membrane [11]. L-type calcium channels are activated by outside-in integrin signalling [3] and thus calcium plays a central role in the control of cell motility.

Proteoglycans As Calcium Chelating Agents

Given that calcium entry into cells is involved in migration it would be anticipated that motility and therefore migration will be sensitive to the availability of calcium ions in the pericellular environment. Hence the presence of calcium chelators in the extracellular matrix can be expected to modify the migratory potential of cells. It is known that certain proteoglycans have powerful ion chelating properties and are therefore potential modifiers of cellular migration. In fact, it is known that the presence of certain proteoglycans in the extracellular matrix act as barriers to migration during embryonic development [12-18]. It is therefore proposed that a plausible explanation for migratory barriers is the presence of calcium chelating proteoglycans. Whilst the precise nature of the ion binding is unclear there is evidence that sulphated polysaccharides are able to bind divalent cations between adjacent chains and the conformation is influenced by the protein interaction [19]. Other possible polysaccharide cation binding modes include the “egg box” and helical models which are also conformationally determined [20,21].

Control of Migration

In the basic domain model, it is proposed that the territorial boundaries of the microenvironmental niches permit cellular exchanges through the process of migration. However, in order to impose structural limits to tissues it is necessary to take account of controls of migration between adjacent domains. It is suggested that migration is capable of regulation by the production of extracellular materials that are able to act as barriers to cell movement. One class of compounds which may function in this manner are calcium-chelating agents such as selected proteoglycans which can act as territorial barriers. The tissue distribution of these territorial barriers will determine architectural features such as those developed during embryogenesis [22].

The simplest arrangement of this kind would involve the local turnover of barrier proteoglycans. If these were synthesised, secreted and degraded by marginal cells (say at the base of epithelia) their local concentration would be autonomously maintained by the cells in question. This may be the origin of basement membrane structures.

These barriers may be selective so that different cells may or may not cross the frontiers between certain domains. Assuming that the effect on cell motility is equivalent for all cells any selectivity of action will depend on the ability of cells to alter the barrier material. Given that the

properties of proteoglycans are regulated by the structural influence of the protein component it is likely that migratory ability is associated with the production of enzymes such as the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) proteinases [23].

Since migratory capability is of central significance to the proliferative success of cancer cells it is probable that a cardinal feature of the malignant phenotype may be the expression of cell surface proteinases [24].

However, since such a mechanism would be unselective in its effect, an alternative proposal is that cells may be differentially sensitive to the local Ca^{++} concentration. Such an arrangement would permit some classes of cell to migrate in localities where others are immobilised, thus giving them a selective advantage in entering new domains. For example, cells overexpressing L-type calcium channels may possess a migratory advantage and there is evidence that many cancer cells manifest high levels of these voltage-gated calcium channels [25].

Article Information

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Keywords

Calcium; cell motility; logistic domains; migration; proliferation; proteoglycans.

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