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Review

Neuronal and metastatic cancer cells: Unlike brothers

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ABSTRACT

During development neuronal cells traverse substantial distances across the developing tissue. In the mature organism, however, they are bound to the confines of the nervous system. Likewise metastatic cancer cells have the potential to establish auxiliary tumor sites in remote tissues or entirely different organs. The epithelial–mesenchymal transition is the transformation of proliferative cancer cells into a highly invasive state, which facilitates the crossing of tissue boundaries and migration across various environments. This review contributes a first look into the parallels and contrasts between physical aspects of neuronal and metastatic cancer cells.

1. Introduction

Even though neuronal and cancer cells have quite different purposes in the body, both must traverse substantial distances in the body. It is not wholly identified why neurons can only navigate within the confines of a defined microenvironment, while cancer cells are able to migrate through diverse settings. Recent studies of these cells have revealed some striking similarities in both form and function of these two unique cell types; however the respective roles of these elements have not been thoroughly considered. Here we review these different findings and inspect which aspects are shared between cancer and neuronal cells and how they employ these features for both dissimilar and shared purposes. Specifically, we examine substrate effects particularly in respect to extracellular matrix (ECM) modifications and constrictions, intracellular mechanics, cellular pushing forces, cytoskeletal filaments, and filopodia of neuron and cancer cells, explaining how these unique cell types achieve their specialized purposes, while sharing a variety of features. This will provide a perspective on cellular flexibility in organisms and could unite efforts in two important applied research fields across a variety of disciplines including biology, physics, chemistry and medicine.

Neuronal cells in the developing brain of most organisms do not come into existence pre-wired but are rather laid out in developmental sheets of cells that must be correctly interconnected for proper neuronal function. In this highly intricate process the soma, or cell body, of neurons extends dendrites and axons; these are responsible for conducting electrical impulses and thereby transmit information. During pathfinding in the developing brain they are headed by a motile cytoskeletal structure composed of a dense actin filament network interspersed with microtubule (MT) filaments and a variety of motor proteins. This dynamic neurite tip is called the growth cone and is responsible for seeking out the neuron's synaptic target. Neurites navigate through dense and heterogeneous tissue, which requires a highly specialized motility apparatus [1]. The distinctive combination of long-range navigation through a crowded and diverse environment and their shared developmental aspects are bridging the extremes between metastatic cancer cells and neurons.

When cancer cells spread from their primary tumor to propagate in remote tissue they form metastases, which is the cause of approximately 90% of cancer-related fatalities [2]. For cancer cells to metastasize several physical changes are required. Initially they have to obtain a migratory phenotype and invade adjacent tissues, while chemotaxis leads them to blood vessels. Here they have to penetrate the compact basement membrane ECM by forming protrusive processes with ECM-degrading function and enter the surrounding endothelial cell barrier in order to intravasate into the lymphatic or blood vessels for transport to remote organs or tissues [3].

While cancerous cells can migrate in diverse surroundings, believed to be attributed to their various potential motility modes during the epithelial–mesenchymal transition (EMT), neurites are constricted to the confines of the nervous system.

2. Substrates

Contrary to most other cell types neurons actually prefer to extend on softer over stiffer substrates (Fig. 1, A), but depending on the nervous

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system type they maneuver through very unlike environments and thereby need to adapt their biomechanics to their surroundings [4].

An example of this can be seen in a study comparing dorsal root ganglion (DRG) cells as a model for the peripheral nervous system (PNS) and hippocampal neurons, which represent neurons of the central nervous system (CNS). It is observed that DRG neurons produce the longest extensions on substrates with a stiffness of ~1000 Pa while higher and lower elasticities reduce outgrowth, whereas hippocampal neurons have a neurite length independent of substrate stiffness. DRGs on soft substrates generate significantly higher forces, while exhibiting greatly reduced retrograde flow rates and stronger cytoskeletal substrate coupling, yet both types of neurons increase their traction forces on stiffer substrates [5].

A similar adaption has also been found in cancer cells, where a variety of cancer cell lines could be categorized as either substrate rigidity-dependent or independent. Substrate stiffness-independent cell lines exhibited no change in growth rate, whereas dependent cell lines displayed increased growth, migration and spreading on stiffer matrices (Fig. 1, B). This stands in stark contrast to other cell types like epithelial, smooth muscle and fibroblasts that are reliant on a narrow range of stiff substrate elasticity for growth. Some of the cell lines that showed a rigidity-dependent growth profile even adapted various hallmarks of the invasive mesenchymal phenotype on stiffer substrates [6].

A possible purpose for this selective behavior is suggested by investigating the originating tissue of these cells, as it has been shown that single cell populations of the MBA-MD231 breast cancer cell line provide characteristic cellular feedback dependent on substrate rigidity. These cancer cells exhibit increased proliferation and invasiveness on substrates with an elasticity and coating comparable to their in vivo metastases sites, an effect known as tissue tropism, suggesting that part of site-specific invasion is determined by local substrate mechanics [7].

Glioblastoma multiforme a highly aggressive cancer of the CNS displays behavior resembling both cancer and neuronal cells depending on ECM rigidity. At low rigidity close to brain tissue (80 Pa) these cells resemble neurons, are largely non-proliferative and display little migration. On stiffer substrates, these cells multiply five-times faster and their migratory speed increases drastically, likely as a result of their transformation from a uniformly rounded morphology with nonfunctional filopodial extensions to a spread and crawling cell [8].

This increased activity on more rigid substrates is also observed in various carcinoma cells: in hepatocellular carcinoma proliferation is increased up to 12-fold on 12 kPa versus 1 kPa matrices, depending on cell type. Treatment with apoptosis-inducing chemotherapeutic drugs showed reduced apoptotic behavior for cells cultured on stiff substrates; however cells cultured on soft matrices had a significantly increased frequency of clone-initiation, a measure of a cell's ability to proliferate indefinitely, pointing to the fact that non-rigid substrates elicit stem cell characteristics in these cells [9].

Increased substrate rigidity can not only stimulate proliferation and chemotherapeutic resistance but also increase cell forces independent of cell spreading, given that the overall net traction forces of both metastatic cells and non-metastatic cells are higher on surfaces having tumor-like stiffness (5 kPa). This could render cell force generation to be a potential candidate as a biomechanical marker for metastatic potential; since metastatic cells exert significantly greater forces than non-metastatic cells, contractile forces can reflect the metastatic phenotype and may function as an in vitro diagnostic [10].

Not all features discussed here might be applicable to cells in 3D in vivo or in vitro environments, since it is plausible that cell form and function might change substantially in this setting.

3. Confinement

Apart from substrate rigidity, other environmental cues transform the motility of neurons and cancer cells. A prominent example of this is the neuron migration along radial glial cells during neurogenesis. This exceptional pathway allows neurons to reach their precise target neuronal layers via enveloping of glial fibers with a leading process, composed of lamellipodia and short filopodia, while the cell assumes a bipolar form and connects the soma to the fiber. This soma-based movement is quite remarkable since neurons in the adult mammalian brain are usually rather stationary, whereas only neurites rearrange themselves [11].

An analogous phenomenon can be observed in certain types of cancer cells whose motility seems to be guided by collagen fibers. Metastatic variations of these cells appear to migrate towards blood vessels and intravasate to eventually form secondary tumors [3]. ECM fiber alignment thus creates motility paths for both neurons and cancerous cells to migrate in a directed way.

In vitro similar tracks for cells can be artificially constructed by creating patterns ranging from 1.5 to 12 μm in grooves, to which various ligand proteins can be applied, which then make up guidance channels. Confining growth cones to these narrow channels of different widths does not alter their movement speed, even though their size adjusts to the channel width. They do however respond to immediate changes in their surroundings, as their extension speed temporarily increased in the nodes between confinement channels. Growth and curiously

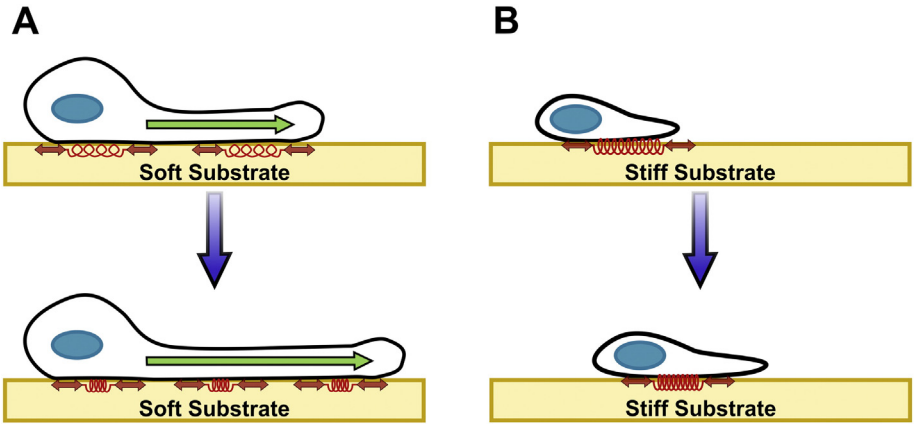

Fig. 1. Diverse motility modes. A) The soft environment on which neurons grow transforms most of the motile forces exerted by the cell into substrate deformation resulting in a fairly static soma. This does not affect growth cone mobility, since it is from this stationary point that stiff microtubules extend into the neurite to provide the pushing forces for translocation. B) On stiff substrates less energy is transferred into substrate deformation, which results in highly motile cancer cells. Not depicted here is the case of cancer cells on soft substrates in which they enter an immobile but highly proliferative state.

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