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Research Article

Cell migration or cytokinesis and proliferation? – Revisiting the "go or grow" hypothesis in cancer cells in vitro

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ABSTRACT

The mortality of patients with solid tumors is mostly due to metastasis that relies on the interplay between migration and proliferation. The "go or grow" hypothesis postulates that migration and proliferation spatiotemporally excludes each other.

We evaluated this hypothesis on 35 cell lines (12 mesothelioma, 13 melanoma and 10 lung cancer) on both the individual cell and population levels. Following three-day-long videomicroscopy, migration, proliferation and cytokinesis-length were quantified. We found a significantly higher migration in mesothelioma cells compared to melanoma and lung cancer while tumor types did not differ in mean proliferation or duration of cytokinesis. Strikingly, we found in melanoma and lung cancer a significant positive correlation between mean proliferation and migration. Furthermore, non-dividing melanoma and lung cancer cells displayed slower migration. In contrast, in mesothelioma there were no such correlations. Interestingly, negative correlation was found between cytokinesis-length and migration in melanoma. FAK activation was higher in melanoma cells with high motility.

We demonstrate that the cancer cells studied do not defer proliferation for migration. Of note, tumor cells from various organ systems may differently regulate migration and proliferation. Furthermore, our data is in line with the observation of pathologists that highly proliferative tumors are often highly invasive.

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Introduction

The mortality of patients with solid tumors is mostly due to the metastatic potential of tumor cells which requires a fine adjustment and a temporal interplay between cell migration and cell proliferation. Based on the concept that genetic and cytoskeletal machineries cannot be used for proliferation and migration concurrently, the "go or grow" hypothesis postulates that migration and cell division are mutually exclusive, and tumor cells defer proliferation for cell migration [2,7,8,35].

Research on mechanisms of tumor cell migration and invasion is in part driven by the need for effective anti-cancer drugs that can also target the survival-prone subpopulation of tumor cells that are able to escape from the primary tumor and survive in metastatic tissue microenvironment. If tumor cells defer cell proliferation for cell migration then migrating cells should have a decreased sensitivity to treatment modalities that target proliferating tumor cells. Conversely, anti-proliferative therapies may select for migratory cells or even induce cell migration in surviving cell populations. Furthermore, inhibiting cell migration might induce the proliferation of disseminating cells and lead to primary or secondary tumor growth. Better understanding of the connection between proliferation and migration is essential for the development of therapies inhibiting both of these cellular processes.

Most studies examining the "go or grow" hypothesis have been performed on intracranial tumor cells of neuroectodermal origin and the data is rather conflicting. A number of studies have demonstrated that proliferation and migration correlate inversely in a variety of tumor types of the central nervous system including gliomas, meningeoma and primitive neuroectodermal tumors [8,18,26,33,37]. In contrast, in medulloblastoma studies, the tumor cells did not defer proliferation for cell migration [2]. Similarly, other studies reported no reciprocal association between proliferation and the migratory activity of glioma cells [22,31,42].

In the context of glioma migration and proliferation, several molecular mechanisms were proposed that identify certain microenvironmental factors that can lead to differential regulation of migration and proliferation. Certain extracellular matrix components, hypoxia and low glucose levels were identified as inducing factors that could lead to this dichotomy through the regulation of FAK expression, the mir451/LKB1/AMPK or mir9/CREB/NF1 signaling and via carboxypeptidase E (CPE) expression, respectively [8,9,15,38].

A number of mathematical models have been developed in order to study the cellular and molecular mechanisms that can underline such a dichotomy [1,6,11,19,41]. Some of the theoretical approaches using stochastic and probabilistic mathematical models could recapitulate similar behavior [6,11] while others challenged certain aspects of the "go or grow" hypothesis [1].

From the structural point of view, during the cytokinetic phase of cell cycle the actin and microtubule cytoskeletal apparatus is used to maintain changes in cell shape and mitotic cell rounding. Consequently, during cell division, the normal cytoskeletal apparatus should not be available for active cell migration [30,36]. The competition of proliferation and migration for the finite free energy [adenosine 5′-triphosphate (ATP)] resources [4] would also support the mutual exclusiveness of these cellular processes.

Since the "go or grow" hypothesis is currently largely based on central nervous system tumors, in this study we present an assessment of the "go or grow" hypothesis in 35 tumor cell lines with neuroectodermal, mesodermal and entodermal origin. In order to characterize the concurrent proliferative and migratory activity of different malignant tumors both at the individual tumor cell and population levels, we used long-term time-lapse videomicroscopy in 2D cell cultures.

Methods

Cell lines

Altogether 35 human cell lines deriving from different cancers with different embryonic origin were used in this study. Thirteen cell lines deriving from malignant melanoma (neuroectodermal origin), 12 cell lines from malignant mesothelioma (mesodermal origin) and 10 lung cancer cell lines (mainly entodermal origin) were investigated. The A2058, A375 and MEWO melanoma cell lines, the CRL5820 and CRL5915 mesothelioma and the H146, H1650, H1975, HTB-182 and SW900 lung cancer cell lines were purchased from ATCC. The WM35, WM983A and WM983B melanoma cell lines were recieved from the Wistar Institute, Philadelphia, USA. The HCC-15 and LCLC103 lung cancer cells were purchased from the Deutsche Sammlung von Mikroorganismen und Zellkulturen (DSMZ; Leibniz Institute, Braunschweig, Germany). The M24met melanoma line, established from an invaded lymph node of a nude mouse [28], was kindly provided by B.M. Mueller (Scripps Research Institute, La Jolla, CA). The melanoma cell lines HT168, HT199 and HT168-M1 were developed in the National Institute of Oncology, Hungary [20,21]. The VM-1, VM-21 and VM-24 melanoma and the VMC23 and VMC33 mesothelioma cell lines were established in the Institute of Cancer Research at Medical University of Vienna. The SPC111, SPC212 and M38K cells were established from biphasic MPMs and were kindly provided by Professor R. Stahel (SPC11 and SPC212, University of Zurich, Zurich, Switzerland) and Professor V.L. Kinnula (M38K, University of Helsinki, Helsinki, Finland). The P31wt and its cisplatin-resistant derivative, P31res (established by in vitro cisplatin selection), were kindly provided by Professor K. Grankvist (University of Umea, Umea, Sweden). The SELS and the EKVX lung cancer cell lines were described in [5,16]. LC42 cells were a kind gift from Professor Ø. Fodstad (Institute for Cancer Research, Oslo, Norway). The I-2 and I-9 MPM cell lines were kindly provided by Professor A. Catania (University of Milano, Milano, Italy).

Cell cultures were maintained in DMEM media (Lonza, Switzerland; with 4500 mg/dm^3 glucose, piruvate and L-glutamine) supplemented with 10% fetal calf serum (Lonza, Switzerland) and 1% penicillin–streptomycin–amphoterycin (Lonza, Switzerland) in tissue culture flasks at 37 °C in a humidified 5% CO_2 atmosphere.

Assessment of migration, proliferation and duration of cytokinesis

Videomicroscopy measurements were carried out as described previously [13,14]. Briefly, cells were plated in the inner eight wells of 24-well plates (Corning Incorporated, USA). Overnight