Am J Physiol Cell Physiol 306: C78–C79, 2014.
First published October 23, 2013; doi:10.1152/ajpcell.00292.2013.

Physical Biology in Cancer. 1. Cellular physics of cancer metastasis

Nicole M. Moore and Larry A. Nagahara

Office of Physical Sciences-Oncology, Center for Strategic Scientific Initiatives, National Cancer Institute, Bethesda, Maryland

Submitted 20 September 2013; accepted in final form 18 October 2013

Moore NM, Nagahara LA. Physical Biology in Cancer. 1. Cellular physics of cancer metastasis. *Am J Physiol Cell Physiol* 306: C78–C79, 2014. First published October 23, 2013; doi:10.1152/ajpcell.00292.2013.—One of the major challenges in cancer research today is developing new therapeutic strategies to control metastatic disease, the spread of cancer cells from a primary tumor to seed in a distant site. Advances in diagnosis and treatment options have increased the survival rate for most patients with local tumors; however, less progress has been made in treatment of disseminated disease. According to the *SEER Cancer Statistics Review, 1975–2010*, in the case of breast and prostate cancers, only one in four patients diagnosed with distant metastatic disease will survive more than five years. Current research efforts largely focus on identifying biological targets, such as specific genes and signaling pathways that drive two key steps of metastasis, invasion from the primary tumor and growth in the secondary site. On the other hand, there are phenotypic traits and dynamics in the metastatic process that are not encoded by single genes or signaling pathways but, rather, a larger system of events and biophysical characteristics. Connecting genomic and pathway investigations with quantitative physical phenotypic characteristics of cells, the physical microenvironment, and the physical spatiotemporal interactions of the metastatic process provides a stronger complementary understanding of the disease.

physics of cancer; cell mechanics; microfluidics

CELLS AND TISSUES TRANSITION through a series of defined changes in their behaviors and phenotypes that are often mediated or accompanied by altered physical properties at the subcellular, cellular, and tissue levels. During metastasis, cancer cells encounter several obstacles, such as negotiating extracellular matrices that vary in topology, invading surrounding cells and tissues with different stiffness, and traversing into or out of vasculature and lymphatic vessels with shear and compressive forces (10). To overcome these barriers, cancer cells undergo transitions that perturb cell processes, such as surface receptor expression, cytoskeleton reorganization, and directional polarity, which ultimately contribute to changes in phenotype. Being able to detect and measure mechanical or phenotypic changes will allow for new understanding of the disease and the development of possible novel therapeutic and diagnostic solutions targeted specifically at physical biomarkers of cancer cells and the microenvironment. Physical scientists and engineers represent major resources for sophisticated investigation of these physics-based parameters and can help us gain a more complete picture of cancer metastasis.

To increase the number of physical scientists and engineers focused on the problem of cancer metastasis, the National Cancer Institute started the Physical Sciences-Oncology Centers (PS-OCs) program. In 2009, 12 PS-OCs were established to form a PS-OCs Network, bringing together, for the first time, teams of experts from the physical and biological sciences to study cancer at a fundamental level (9). One of four thematic areas of the program is dedicated to understanding the physics of cancer. This includes how forces, diffusion/transport of molecules and energy, electrical potentials, and thermodynamic stability, may affect cancerous and normal states at all length scales and contribute to the spatiotemporal complexity of cancer and its treatment. Integration of engineered devices with physics, molecular biology, and imaging techniques has resulted in new insights into the metastatic process, specifically, the physical forces and geometry important to tumor cell adhesion and migration mechanisms.

Research from the PS-OCs associated with the physics of cancer is highlighted in the review articles in this special issue.[1] Several PS-OCs have used novel technologies to investigate the physical characteristics of circulating tumor cells (CTCs), including stiffness, adhesion, rolling, and coagulation, during the metastatic cascade. At the Cornell University PS-OC, Mike King and colleagues have used advanced microfluidic technology to understand and exploit the physical properties of CTCs. CTC capture devices were designed based on the cell volume of CTCs relative to other cells to increase the contact area with capture microposts and decrease nonspecific interactions (5). The use of functionalized microtubes has enabled detailed understanding of physical cell conditions that increase the probability of cancer cell rolling and adhesion to the endothelium during extravasation (2). Owen McCarty

Address for reprint requests and other correspondence: N. M. Moore, Office of Physical Sciences-Oncology, Center for Strategic Scientific Initiatives, National Cancer Institute, 9000 Rockville Pike, Bethesda, MD 20892 (e-mail: moorenm@mail.nih.gov).

[1] This review is part of a five-article theme series on Physical Biology in Cancer in this issue.

and colleagues at the Scripps Research Institute PS-OC are using novel light-scattering and microscopy single-cell analysis techniques to study the unique physical properties of CTCs, such as volume and density, and correlate these features to localization and formation of secondary tumors as well as tumor embolisms (7, 8).

In addition to studying CTCs, several groups have investigated the interplay of physical characteristics of invasive cells and the surrounding microenvironment. Konstantinos Konstantopoulos and colleagues at the Johns Hopkins University PS-OC employed a confined microchannel system to depict one-dimensional migration of cancer cells in confined spaces, representing a more physiological measure of migration in vivo (4). They found that cells adopt distinct signaling strategies to modulate cell migration in different geometries. Cynthia Reinhart-King and colleagues at the Cornell University PS-OC is investigating how the physical characteristics of tumor cells contribute to invasion from the primary tumor. Using techniques such as traction force microscopy and tissue-engineered coculture systems that recapitulate heterogeneous cell-cell interactions, they found that cells with higher traction force display a higher invasive phenotype and induce the collective invasion of less invasive cells by creating microchannels (1, 6). This new knowledge of the complex interplay between the physical properties of the cells and the microenvironment complements existing information of signaling networks and provides a broader picture of the metastatic process.

This special issue of the *American Journal of Physiology-Cell Physiology* gathers reviews that examine various aspects of cancer, incorporating a novel physical/engineering perspective to understanding cancer metastasis. These reviews cover a wide range of relevant length scales (molecule to organ) and highlight new tools and approaches to explore the physical characteristics of cancer metastasis.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

N.M.M. and L.A.N. drafted the manuscript; N.M.M. and L.A.N. edited and revised the manuscript; N.M.M. and L.A.N. approved the final version of the manuscript.

REFERENCES

1. **Carey SP, Starchenko A, McGregor AL, Reinhart-King CA.** Leading malignant cells initiate collective epithelial cell invasion in a three-dimensional heterotypic tumor spheroid model. *Clin Exp Metas* 30: 615–630, 2013.
2. **Geng Y, Chandrasekaran S, Hsu JW, Gidwani M, Hughes AD, King MR.** Phenotypic switch in blood: effects of pro-inflammatory cytokines on breast cancer cell aggregation and adhesion. *PLos One* 8: e54959, 2013.
3. **Howlader NN, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA.** (Editors). *SEER Cancer Statistics Review, 1975–2010*. National Cancer Institute, Bethesda, MD. http://seer.cancer.gov/csr/1975_2010/ [November 2012].
4. **Hung WC, Chen SH, Paul CD, Stroka KM, Lo YC, Yang JT, Konstantopoulos K.** Distinct signaling mechanisms regulate migration in unconfined versus confined spaces. *J Cell Biol* 202: 807–824, 2013.
5. **Kirby BJ, Jodari M, Loftus MS, Gakhar G, Pratt ED, Chanel-Vos C, Gleghorn JP, Santana SM, Liu H, Smith JP, Navarro VN, Tagawa ST, Bander NH, Nanus DM, Giannakakou P.** Functional characterization of circulating tumor cells with a prostate-cancer-specific microfluidic device. *PLos One* 7: e35976, 2012.
6. **Kraning-Rush CM, Califano JP, Reinhart-King CA.** Cellular traction stresses increase with increasing metastatic potential. *PLos One* 7: e32572, 2012.
7. **Phillips KG, Kolatkar A, Rees KJ, Rigg R, Marrinucci D, Luttgen M, Bethel K, Kuhn P, McCarty OJ.** Quantification of cellular volume and sub-cellular density fluctuations: comparison of normal peripheral blood cells and circulating tumor cells identified in a breast cancer patient. *Front Oncol* 2: 96, 2012.
8. **Phillips KG, Velasco CR, Li J, Kolatkar A, Luttgen M, Bethel K, Duggan B, Kuhn P, McCarty OJ.** Optical quantification of cellular mass, volume, and density of circulating tumor cells identified in an ovarian cancer patient. *Front Oncol* 2: 72, 2012.
9. **Physical Sciences-Oncology Centers Network.** A physical sciences network characterization of non-tumorigenic and metastatic cells. *Sci Rep* 3: 1449, 2013.
10. **Wirtz D, Konstantopoulos K, Searson PC.** The physics of cancer: the role of physical interactions and mechanical forces in metastasis. *Nat Rev Cancer* 11: 512–522, 2011.