5th Micro and Nano Flows Conference
Milan, Italy, 11-14 September 2016

Microfluidic Models of Metastatic Cancer

Roger D. KAMM [1,*]

* Corresponding author: Tel.: +01 617-253-5330; Email: rdkamm@mit.edu
1 Departments of Biological Engineering and Mechanical Engineering, Massachusetts Institute of Technology, USA

Keywords: Microfluidics, Cancer, Disease Models, 3D Cell Culture

Over the past 10 years, our ability to realistically model the critical biological steps in disease have dramatically improved, due in large part to the advances in microfluidic technologies. In particular, the capabilities to create realistic 3D microenvironments, including microvascular perfusion, have led to in vitro models for disease that offer considerable advantages over in vivo experiments. In this talk, I will present some recent advances in modeling the successive stages of metastatic cancer, especially in the context of immunotherapies and organ-specific models of metastasis.

1 Setting the Stage

Cancer metastasis progresses through a cascade of events, beginning with the separation of tumor cells from the primary tumor into the surrounding tissue where they experience changes in matrix stiffness, interstitial flows, and biochemical signaling, all of which influence their ability to migrate away from the tumor, either individually or in clusters. In order to create a secondary tumor in a remote organ, the cells need to gain access to the circulatory system, which they do either via the lymphatics or by direct intravasation into a small local blood vessel. There, they are convected by the blood flow first to the lung, and subsequently to other the organs of the body. Due to their size, tumor cells become lodged in the smallest capillaries, where they can either become activated to escape into the surrounding tissue, grossly deform in order to pass through, or succumb to the actions of blood shear stress or interactions with other circulating cells in the blood. Escape from the vasculature poses a challenge due to the tight junctions of the vascular wall. Cancer cells escape, however, by extravasating: sending projections between neighboring endothelial cells, adhering to the subendothelial matrix, and pulling themselves through by acto-myosin contractions. Once in the local tissue, they then can revert to a non-migratory phenotype, begin to proliferate and establish a secondary tumor.

2 The Role of Microfluidics

Historically, cancer metastasis been studied primarily in animal models, due to the critical need for multiple cell types, the essential role of the vasculature, and the 3D nature of the tissues involved in each stage. Microfluidic technologies can effectively be brought to bear in this situation, however, and their application has led to a variety of models that incorporate many of these key features, either singly or in combination. Subsequently, this work has begun to provide new insights into disease progression. Included among these are models of:

(1) Dispersion of cells from a primary tumor, either in empty matrix or in the presence of macrophages [1].
(2) Migration through matrix under the influence of interstitial flow [2].
(3) Migration through ECM in the presence of macrophages [3].
(4) Intravasation from tissue across an intact endothelium [4].
(5) Adhesion to an endothelial monolayer under shear flow conditions [5].
(6) Extravasation across an intact monolayer either into empty matrix or cell-seeded matrix to mimic a particular organ [6].

3 Organ-Specific Models

It is well-known that specific tumors have a propensity to metastasize to particular organs, yet the causes for this are virtually unknown. Our group has begun to probe this issue by seeding organ-specific cells into matrix. For example, we find that breast cancer calls home preferentially to matrix containing MSC-derived osteoblasts over a muscle-mimicking tissue containing a myoblast cell line. We further demonstrated that one of the factors responsible for the low rates of extravasation to muscle is adenosine, which binds to the A_3 adenosine receptor on the breast cancer cells.

4 Models of Immunotherapy

Tremendous interest has developed in the use of the body's own immune system to treat cancer, both primary and metastatic, yet these treatments tend not to be universally effective, and current methods to identify the responsive subpopulation have met with only limited success. Microfluidic models may be useful in identifying the response of a particular patient by introducing patient-derived samples taken from biopsy into a device and using this to screen for effective therapies. Alternatively, microfluidic models can be used to better understand the role of engineered immune cells such at T-cells or NK-cells, and to test for their efficacy in 3D, organ-specific environments, using microfluidics to recapitulate aspects of the in vivo condition.

5 References

[1] Aref AR, Huang RY-J, Yu W, Chua K-N, et al.. Integr Biol (Camb). 2013 Feb;5(2):381-9.
[2] Polacheck WJ, German AE, Mammoto A, Ingber DE, Kamm RD. Proc Natl Acad Sci USA. 2014 Feb 18;111(7):2447-52.
[3] Bai J, Adriani G, Dang TM, Tu TY, Penny HL, Wong SC, Kamm RD, Thiery JP. Oncotarget. 2015 Jul 30.
[4] Zervantonakis IK, Hughes-Alford SK, Charest JL, Condeelis JS, Gertler FB, Kamm RD. Proc Natl Acad Sci U S A. 2012 Aug 21;109(34):13515-20.
[5] Chen MB, Whisler JA, Jeon JS, Kamm RD. Integr Biol (Camb). 2013 5(10):1262-71.
[6] Jeon JS, Bersini, S; Gilardi, M; Dubini, G; Charest, JL; Moretti, M; Kamm, RD; Proc Natl Acad Sci USA, pp. 201417115, 2014