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Review

Advanced biomaterials and microengineering technologies to recapitulate the stepwise process of cancer metastasis

Nitish Peela [a, 1], Danh Truong [a, 1], Harpinder Saini [a, 1], Hunghao Chu [b], Samaneh Mashaghi [b], Stephanie L. Ham [c], Sunil Singh [c], Hossein Tavana [c], Bobak Mosadegh [b], Mehdi Nikkhah [a, *]

[a] School of Biological and Health Systems Engineering (SBHSE), Arizona State University, Tempe, AZ, 85287, USA
[b] Department of Radiology, Dalio Institute of Cardiovascular Imaging, New York-Presbyterian Hospital, and Weill Cornell Medicine, New York, NY, 10021, USA
[c] Department of Biomedical Engineering, The University of Akron, Akron, OH, 44325, USA

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ABSTRACT

Cancer is one of the leading causes of death globally according to the World Health Organization. Although improved treatments and early diagnoses have reduced cancer related mortalities, metastatic disease remains a major clinical challenge. The local tumor microenvironment plays a significant role in cancer metastasis, where tumor cells respond and adapt to a plethora of biochemical and biophysical signals from stromal cells and extracellular matrix (ECM) proteins. Due to these complexities, there is a critical need to understand molecular mechanisms underlying cancer metastasis to facilitate the discovery of more effective therapies. In the past few years, the integration of advanced biomaterials and microengineering approaches has initiated the development of innovative platform technologies for cancer research. These technologies enable the creation of biomimetic *in vitro* models with physiologically relevant (i.e. *in vivo*-like) characteristics to conduct studies ranging from fundamental cancer biology to high-throughput drug screening. In this review article, we discuss the biological significance of each step of the metastatic cascade and provide a broad overview on recent progress to recapitulate these stages using advanced biomaterials and microengineered technologies. In each section, we will highlight the advantages and shortcomings of each approach and provide our perspectives on future directions.

1. Introduction

Cancer is currently the second leading cause of death in the United States claiming the lives of over half a million Americans annually [1]. Poor patient prognosis and treatment outcomes are in large part due to the biological complexities of this devastating disease [2–5]. Cancer metastasis progresses through a stepwise cascade of events, including tumor growth (Fig. 1A), angiogenesis, stromal invasion, intravasation (Fig. 1B), extravasation, and colonization at secondary sites within the body (Fig. 1C) [3]. It is well recognized that the tumor microenvironment plays a substantial role in the metastatic process through dynamic biochemical and biophysical signaling cues. Due to these complexities, there is an overwhelming need to develop a fundamental understanding of cancer metastasis [4–10].

Animal models have been instrumental for studying the cellular and molecular basis of the metastatic process [11,12]. However, due to the presence of confounding factors and physiological variability between humans and animals, it has been challenging to evaluate cause-and-effect relationships between specific biological cues and the resulting cancer cell behavior [13,14]. In particular, these differences have led to failures in translational research towards therapeutic drug development [12]. Additionally, the effectiveness of anti-cancer drugs can substantially vary among patients due to heterogeneities in their molecular profiles [15]. Thus, there has been a heightened initiative to develop *in vitro* tumor models that closely mimic cancer pathophysiology, thereby providing more predictive platforms for personalized medicine.

* Corresponding author.
E-mail address: mnikkhah@asu.edu (M. Nikkhah).
[1] Equal Contribution.

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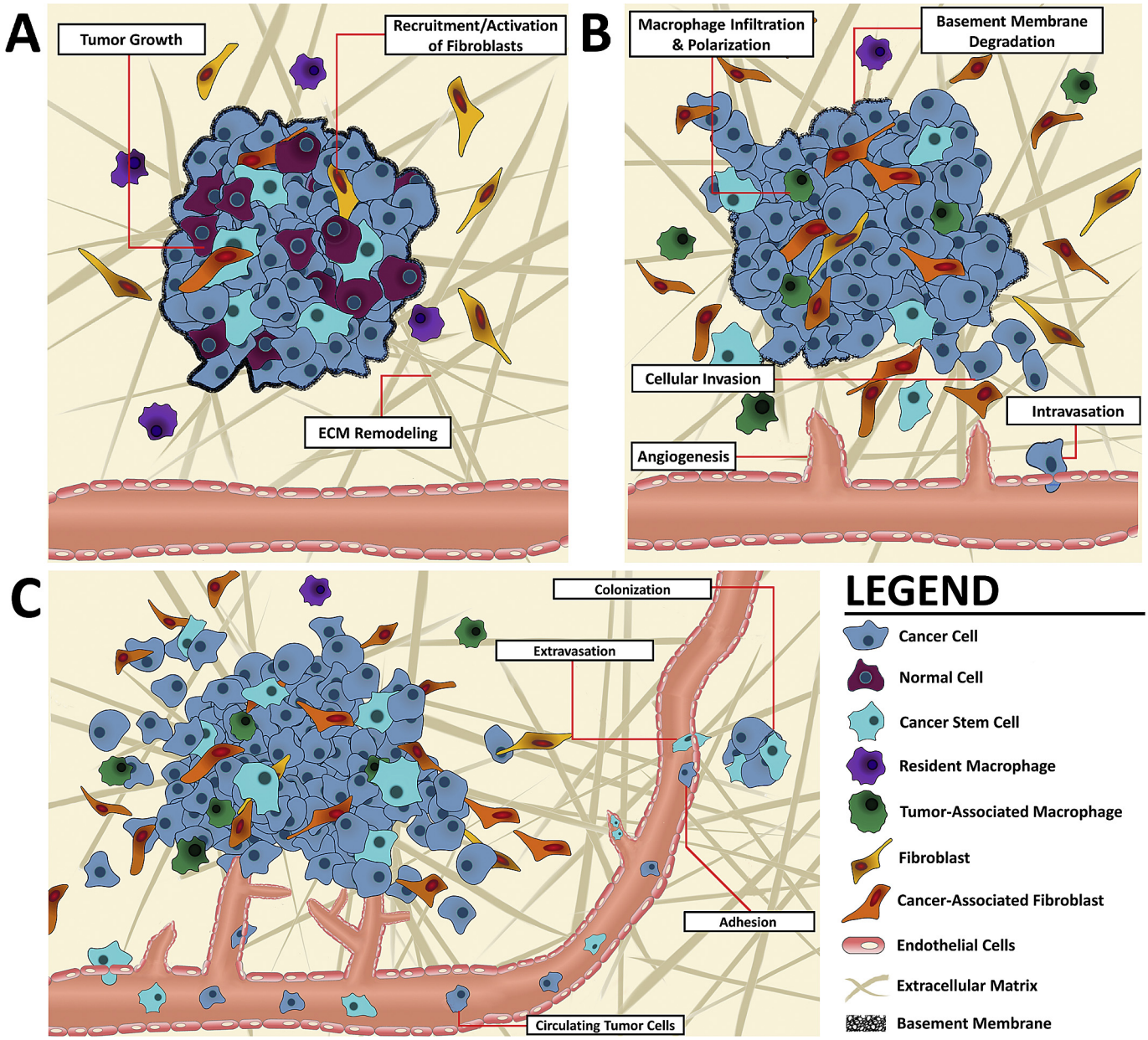

Fig. 1. (A) Schematic of the metastatic cascade. Tumor growth and development results in ECM remodeling as well as differentiation of cancer stem cells and fibroblasts. (B) Subsequently, angiogenesis, cancer cell invasion, and intravasation occur. (C) Finally, surviving cancer cells and cancer stem cells circulate through the body, attach to blood vessels, and extravasate to form secondary metastases.

To date, *in vitro* three-dimensional (3D) culture models (e.g. spheroids and cell-laden hydrogels) have been widely utilized to represent individual steps of the metastatic cascade [13–16]. Contrary to conventional two-dimensional (2D) assays, encapsulation of cancer cells within 3D biomaterials better recapitulates several aspects of the *in vivo* tumor microenvironment with more precise control over biophysical and biochemical signaling cues [17]. Specifically, cancer cells grown in 3D matrices self-organize similarly to their *in vivo* architecture [16,18]. These models also enable studies with physiologically relevant gene/protein expression, gradients of small molecules/cytokines, and autocrine/paracrine signaling [17]. However, a critical component in the development of 3D models is synthesis and selection of proper scaffolding biomaterials that closely recapitulate the native tumor extracellular matrix (ECM).

Natural biomaterials, such as collagen and basement membrane extracts (e.g. matrigel), have been widely utilized in cancer related studies due to their abundance within the native tumor microenvironment [19,20]. Additionally, the relative bioactivity of these materials provides instructive cues that promote a similar cytoarchitecture to the *in vivo* organization [19,20]. However, the use of natural matrices is associated with batch-to-batch variability and limited control over material properties (e.g. stiffness, matrix architecture) [20]. For instance, extracting basement membrane proteins from different *in vivo* locations (e.g. adipose tissue, parenchymal tissue) leads to inconsistent protein composition of the matrix [21] and variability in their mechanical and biochemical properties [22]. Consequently, natural matrices have a defined physical architecture that cannot easily be tailored to study the influences of biophysical cues on tumor progression. Alternatively, synthetic biomaterials enable precise tunability of biophysical