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Review

Organ-on-chip models of cancer metastasis for future personalized medicine: From chip to the patient

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ABSTRACT

Most cancer patients do not die from the primary tumor but from its metastasis. Current *in vitro* and *in vivo* cancer models are incapable of satisfactorily predicting the outcome of various clinical treatments on patients. This is seen as a serious limitation and efforts are underway to develop a new generation of highly predictive cancer models with advanced capabilities. In this regard, organ-on-chip models of cancer metastasis emerge as powerful predictors of disease progression. They offer physiological-like conditions where the (hypothesized) mechanistic determinants of the disease can be assessed with ease. Combined with high-throughput characteristics, the employment of organ-on-chip technology would allow pharmaceutical companies and clinicians to test new therapeutic compounds and therapies. This will permit the screening of a large battery of new drugs in a fast and economic manner, to accelerate the diagnosis of the disease in the near future, and to test personalized treatments using cells from patients. In this review, we describe the latest advances in the field of organ-on-chip models of cancer metastasis and their integration with advanced imaging, screening and biosensing technologies for future precision medicine applications. We focus on their clinical applicability and market opportunities to drive us forward to the next generation of tumor models for improved cancer patient theranostics.

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1. Introduction

Most cancer deaths result from metastasis. Metastasis is defined as the sequence of events leading to the spread of cancer cells from the site of primary tumor to new locations in the human body. A lot of investigation is being carried out into the molecular basis of tumor growth and dissemination [1]. However, the mechanism of metastasis is still poorly understood [2,3]. In addition to genetic and external environmental factors, tumor expansion is also determined by the structural properties of the tumor microenvironment [4]. The details on the mechanism of conversion of a physical stimulus in the tumor microenvironment, such as cell-cell/extracellular matrix (ECM) interactions or fluid shear forces, into a biochemical response during tumor progression are not well understood. Thus, the comprehension of the disease and its progression into metastasis is still limited [5–8]. Metastasis is also related to mechanism of drug resistance which still remains unclear [9–11]. Multiple efforts are directed toward the development of cancer metastasis models that can help in understanding the disease and in the development of innovative therapeutic strategies. Traditionally, standard *in vivo* and *in vitro* models are used to elucidate the mechanisms involved in metastasis [12–17]. The complexity encountered in humans is reproduced with higher fidelity using *in vivo* models. However, the individual contribution of

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Abbreviations

2D	Two-dimensions
3D	Three-dimensions
CAFs	Cancer Associated Fibroblasts
CTCs	Circulating Tumor Cells
ctDNA/RNA	Circulating Tumor DNA/RNA
EBM-2	Endothelial Basal Medium − 2
EC	Endothelial Cells
ECM	Extracellular Matrix
EGFR	Epidermal Growth Factor Receptor
EMT	Epithelial-to-Mesenchymal Transition
EpCAM	Epithelial Cell Adhesion Molecule
FBS	Fetal Bovine Serum
GMP	Good Manufacturing Practice
HER2	Human Epidermal Growth Factor Receptor 2
HUVEC	Human Umbilical Vein Endothelial Cells
IRF-8	Interferon Regulatory Factor − 8
LECs	Lymphatic Endothelial Cells
MoC	Metastasis-on-Chip
PTEN	Phosphatase and Tensin Homolog
R&D	Research and Development
STORM	Stochastic Optical Reconstruction Microscopy
TEM	*Trans*-Endothelial Migration
TNF-α	Tumor Necrosis Factor-α
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell

interconnected physical and biochemical parameters in an *in vivo* model cannot be assessed easily. In addition, they fail in predicting the clinical efficacy of new drug candidates [18,19]. The *in vitro*, though fully controllable, lack the hierarchical complexity of the tumor niche needed to reproduce the native scenario. This threatens the relevance of the data obtained using *in vitro* models. Pre-clinical experimentation demands highly sophisticated and physiologically relevant *in vitro* models capable of recapitulating both the biomolecular and structural properties of the tumor niche along with the dynamic events occurring during the propagation of cancer. In this regard, organ-on-chip technology can be used to design biomimetic microfluidic devices containing human cells to replicate fundamental functional units of human tissues and organs *in vitro* [20–23]. Applied to cancer research, organ-on-chip models of cancer metastasis, or metastasis-on-chip (MoC) emerge as a promising methodology for studying the disease under physiological-like conditions [24].

MoC models provide multiple advantages compared to their *in vitro* and *in vivo* counterparts, which have many barriers for their clinical applications. During the last decade, MoC models have been used to study the contribution of the mechanical and biochemical cues in tumor dissemination, including the impact of cell-cell/stroma interactions [12,25–27], or cytokine gradients [28], among others. Similarly, several events described in the metastasis cascade have been successfully reproduced. This includes cancer cell invasion, angiogenesis, intravasation, extravasation, colonization, and most importantly, the impact of circulating tumor cells (CTCs) in tumor dissemination. Several MoC models have been developed toward their early detection, capturing, analysis and use for exploring their diagnostic and prognostic potential [29]. This is critically important because CTCs are responsible for most cancer-related deaths [30–33].

This review describes the latest and most relevant advances in MoC models, their main advantages, limitations, and future perspectives for cancer research. We anticipate that this new generation of tumor models will provide new insights into the molecular and mechanical mechanisms of metastasis, which have remained elusive due to the limitations of current models. Further, when combined with advanced imaging, sensing and screening techniques, MoC models may be employed to understand the mechanism of targeted drug delivery *in vitro*, improving the knowledge on current treatments and potentially developing new therapeutic avenues [34]. Finally, the translation of MoC models into the pharmaceutical and healthcare market will require MoC models to display unprecedented capabilities. This new generation of tumor models will univocally contribute to improve the prognosis of cancer patients reducing the cost in the healthcare system.

2. Current cancer metastasis models: an overview

A large plethora of cancer metastasis models have been described in the literature during the last years. These *standard* models include both experimental (*in vitro* and *in vivo*) and computational (*in silico*) approaches, which have provided valuable insights into the mechanistic determinants of the disease. They have been extremely useful for studying tumor dissemination, screening anti-cancerous drugs, or testing novel therapeutic strategies. However, they also display serious limitations. In the following, we briefly describe the most common and recent models used to investigate cancer metastasis, analyzing their field of applications, advantages, and limitations. For detailed information on the use of the different models, readers are referred to the references herein.

2.1. In vitro two-dimensional models

Typically, cancer metastasis investigations have been undertaken using standard two-dimensional (2D) models, including standard cell culture dishes, flasks, or multi-well plates (Table 1) [35]. These models offer multiple advantages in comparison to their *in vivo* counterparts. For example, they are simple, cheap, offer easy manipulation, and display high imaging capability (see Fig. 1a). They are also very valuable for the screening and validation of anti-cancerous drugs which are currently being used in clinical therapies [13]. Indeed, 2D models have provided key insights about the mechanistic determinants of cancer cell adhesion and migration, a fundamental feature of tumor dissemination. As an example, the change in the adhesive properties of tumors seeded on culture plates coated with ECM protein can be used to assess which adhesion receptors are involved in the interaction between specific tumor cells and the ECM [36]. However, the simplicity of this type of assay may mask the actual behavior of cells as recently demonstrated using micro/nano-patterns of ECM proteins. In this work, two isogenic populations of ovarian cancer cells showed different behavior in flat or patterned conditions [37]. While in the former cells displayed indistinguishable migration characteristics, their motilities were highly different on patterned substrates.

Two-dimensional assays are typically conducted to study the migratory dynamics of cancer cells. There is clear evidence that cancer cells migrate directionally towards leaky blood vessels as a consequence of (bio)chemical gradients. This process known as *chemotaxis* have been widely studied using 2D *in vitro* models, and

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