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Bioengineering 3D environments for cancer models ☆

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ABSTRACT

Tumor development is a dynamic process where cancer cells differentiate, proliferate and migrate interacting among each other and with the surrounding matrix in a three-dimensional (3D) context. Interestingly, the process follows patterns similar to those involved in early tissue formation by accessing specific genetic programs to grow and disseminate. Thus, the complex biological mechanisms driving tumor progression cannot easily be recreated in the laboratory. Yet, essential tumor stages, including epithelial–mesenchymal transition (EMT), tumor-induced angiogenesis and metastasis, urgently need more realistic models in order to unravel the underlying molecular and cellular mechanisms that govern them. The latest implementation of successful 3D models is having a positive impact on the fight against cancer by obtaining more predictive systems for pre-clinical research, therapeutic drug screening, and early cancer diagnosis. In this review we explore the latest advances and challenges in tumor tissue engineering, by accessing knowledge and tools from cancer biology, material science and bioengineering.

Contents

1. Introduction

1.1. Paradigm shift: mimicking tumor progression through the third dimension

Understanding the underlying biology in tumor initiation and progression is the first step to a successful breakthrough in the development of new and efficient cancer therapies. To achieve this goal, the complex cellular microenvironment needs to be deconstructed into simpler and more predictable systems. This approach helps researchers to identify and analyze the role of key chemical, mechanical and/or physical factors that might drive human pathophysiology.

Abbreviations: EMT, epithelial–mesenchymal transition; ECM, extracellular matrix; 2D, two-dimensional; 3D, three-dimensional; PEG, polyethylene glycol; PLG, poly(lactide-co-glycolide); PLA, polylactic acid; RGD, arginine–glycine–aspartate peptide sequence; MMPs, matrix metalloproteinases; KLD12, KLDLKLDLKLDL self-assembling peptide; RAD16-I, RADARADARADARADA self-assembling peptide; FAK, focal adhesion kinase; AV, arterio-venous; PDMS, polydimethylsiloxane; FDA, Food and Drug Administration; NCI, National Cancer Institute; HTS, high throughput screening.

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Following this framework, cancer research has traditionally relied on two-dimensional (2D) cultures [1,2]. However, it is commonly accepted that cells grow in non-physiologically constrained conditions on these surfaces. In particular, cells are attached to rigid and flat substrates, which force them to polarize and increase their exchange area to culture media. As a consequence, they are subjected to excessive nutrition and oxygenation and molecular gradients cannot be reproduced. Furthermore, production of extracellular matrix (ECM) proteins is strongly modified – in composition, configuration and amount – due to differences in the surface receptors' orientation and clustering and, consequently, cells do not receive the proper signals that arise from natural ECM configuration [3–5]. Specifically in the field of cancer, poorly adherent cells – metastatic cells – cannot form tight focal adhesions and, as a consequence, are not easily cultured in classical cell culture dishes. The outcome obtained with metastatic cells in drug screening processes under 2D culture conditions is limited [6]. 2D cultures also activate an immortalization process through multiple passages, which result in the selection of cancer cells that rapidly proliferate. These cells misrepresent the whole tumor, since they are specifically susceptible to therapies that target rapidly dividing cells [7].

To avoid these experimental inconsistencies, it is essential to develop models with a higher degree of complexity while retaining the reproducibility and the capacity of cellular level imaging. First steps have been focused on the generation of multicellular spheroids, which have taken cancer biology to the third dimension (3D) and exemplified the application of biomimetic principles in research. Spheroid cultures partially reestablish 3D tumor architecture patterns since they create hollow cores that contain quiescent and hypoxic cells. Interestingly, spheroids exhibit greater anticancer drug resistance as compared to conventional monolayer cultures [8,9]. However, they have important limitations since they grow as independent cellular aggregates and show reduced interactions with the extracellular milieu [3,10]. Considering that microenvironment controls tumorigenesis, ECM analogs have been introduced as cell culture systems in order to embed cells in a 3D context and display the appropriate physical, chemical and mechanical cues for cell fates (Fig. 1). Pioneering work has been based on the use of biomaterials from natural origins, principally Matrigel and collagen. Experiments have revealed that phenotypical differences between malignant and normal epithelial cells can be exclusively observed in 3D cultures, in which malignant cells lose tissue polarity and organization, phenomena not commonly detected in 2D. Therefore, the remarkable plasticity of cancer cells under different experimental conditions can be easily reproduced by using 3D cultures, which enable reestablishment in vitro of crosstalk among neighboring cells and their surrounding stroma [11–13].

Cancer research has experienced a paradigm shift during the past two decades. However, many groups from academia and the biomedical industry still routinely use 2D cultures, which provide unreliable data and, thus, hamper the discovery and therapeutic assessment of cancer drugs [14,15]. Multiple data illustrate the slow progress in cancer drug research and development. It is estimated that a 10 to 12 year cycle is needed to develop a new cancer drug and candidates that enter clinical trials have only a 5% probability of receiving approval from the U.S. Food and Drug Administration (FDA) [1,7,16]. 3D cultures may be a viable alternative to expedite the process from bench to bedside. The appropriate model design should help to identify key factors regulating tumor development such as cell–matrix interaction receptors (i.e. integrins), cell–cell interaction receptors (i.e. cadherins) and cell growth factor receptors as well as other modulators. As a result, the arsenal of cancer therapeutics would strongly increase based on better-characterized signaling pathways related to the surrounding tumor microenvironment that may be used as new therapeutic targets. Furthermore, 3D models can also help in gaining a deeper understanding of the mechanisms that confer multidrug resistance (expression of efflux transporters, deregulation of cellular metabolism involving DNA repair, apoptosis or cell cycle signaling and decrease drug uptake) and, as a consequence, develop drugs capable of engaging, evading or exploiting them [17,18]. In this review, we describe the most representative 3D bioengineered models for cancer, applying state of the art bioengineering and biomaterial tools.

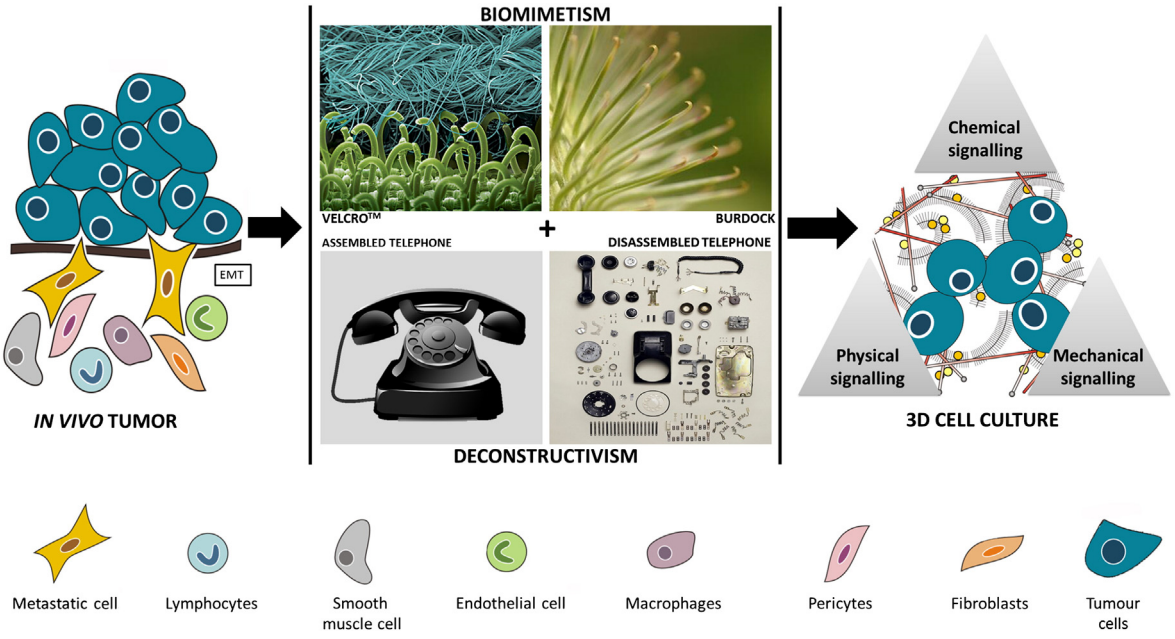

Fig. 1. Bioengineers have developed ECM analogs as 3D culture systems, applying biomimetism and deconstructivism as design principles, in order to produce valuable models that help to better comprehend disease pathogenesis of tumors. Nature is used as a source of ideas to obtain biomaterials that can mimic as closely as possible the physical, chemical and mechanical signals that arise from the ECM (biomimetism). Due to the complexity and interaction among these variables, tissue engineering focuses on deconstructing the in vivo cellular microenvironment into simpler and predictable models that enable the analysis and identification of the environmental signals that rule tumor initiation and progression (deconstructivism). Image of a disassembled telephone courtesy of J. P. Wiegmann and My Modern Metropolis.

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