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Three-dimensional *in vitro* tumor models for cancer research and drug evaluation

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ABSTRACT

Cancer occurs when cells acquire genomic instability and inflammation, produce abnormal levels of epigenetic factors/proteins and tumor suppressors, reprogram the energy metabolism and evade immune destruction, leading to the disruption of cell cycle/normal growth. An early event in carcinogenesis is loss of polarity and detachment from the natural basement membrane, allowing cells to form distinct three-dimensional (3D) structures that interact with each other and with the surrounding microenvironment. Although valuable information has been accumulated from traditional *in vitro* studies in which cells are grown on flat and hard plastic surfaces (2D culture), this culture condition does not reflect the essential features of tumor tissues. Further, fundamental understanding of cancer metastasis cannot be obtained readily from 2D studies because they lack the complex and dynamic cell–cell communications and cell–matrix interactions that occur during cancer metastasis. These shortcomings, along with lack of spatial depth and cell connectivity, limit the applicability of 2D cultures to accurate testing of pharmacologically active compounds, free or sequestered in nanoparticles. To recapitulate features of native tumor microenvironments, various biomimetic 3D tumor models have been developed to incorporate cancer and stromal cells, relevant matrix components, and biochemical and biophysical cues, into one spatially and temporally integrated system. In this article, we review recent advances in creating 3D tumor models employing tissue engineering principles. We then evaluate the utilities of these novel models for the testing of anticancer drugs and their delivery systems. We highlight the profound differences in responses from 3D *in vitro* tumors and conventional monolayer cultures. Overall, strategic integration of biological principles and engineering approaches will both improve understanding of tumor progression and invasion and support discovery of more personalized first line treatments for cancer patients.

Contents

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Introduction

Cancer is the major cause of death worldwide, and one in every four deaths in the United States is due to cancer-related diseases (Siegel et al., 2012). While cells in normal tissue reside in defined locations and maintain steady numbers, cancer cells remove these constraints through mutations in oncogenes and tumor suppressor genes (Esmaeilsabzali et al., 2013; Joyce and Pollard, 2009). Consequently, cells in the tumor tissues can sustain proliferative signaling, evade growth suppressors, resist cell death, enable replicative immortality, induce angiogenesis, and activate invasion and metastasis (Hanahan and Weinberg, 2011). During cancer progression and metastasis, malignant cells maintain their close interactions with surrounding cells and the stromal extracellular matrices (ECM) (Fig. 1) (DelNero et al., 2013; Hanahan and Weinberg, 2011; Infanger et al., 2013; Nyga et al., 2011; Seo et al., 2013). Numerous stromal cells, including endothelial cells of the blood and lymphatic circulation, stromal fibroblasts, and innate and adaptive infiltrating immune cells together comprise the complex tumor microenvironment (Hanahan and Weinberg, 2011; Joyce and Pollard, 2009; Koontongkaew, 2013). The stromal ECM is composed of complex assemblies of collagens, glycosaminoglycans and proteoglycans and the molecules that bind to them (Jain, 1999; 2012). Tumor cells interact with those stromal components dynamically through growth factor-mediated tumor-stromal cell crosstalk (Murata et al., 2011) and integrin-mediated tumor-ECM interactions (Desgrosellier and Cheresh, 2010). Moreover, these interactions evolve along with the progression of the disease (Tlsty and Coussens, 2006), where the stromal microenvironment can initially exert inhibitory effects on even aggressive malignant tumor cells (Bissell and Hines, 2011; Joyce and Pollard, 2009; Xu et al., 2012a). However, as the disease progresses, cancer cells exploit and modify their surroundings to facilitate the inappropriate growth, angiogenesis, invasion and ultimately metastasis in a secondary site (Chung et al., 2012; Joyce and Pollard, 2009; Psaila and Lyden, 2009). In general, tumor growth and progression require intricate interactions between cancer cells and their surrounding microenvironment.

In vitro studies aimed at gaining molecular understanding of cancer progression or the identification of effective anti-cancer therapeutics rely on the availability of a versatile platform that closely recapitulates pathophysiological features of the native tumor tissue and its surrounding microenvironment. Conventional two dimensional (2D) platforms (Hutmacher et al., 2010) are well established and straightforward to use. However, the absence of the third dimension can obscure the

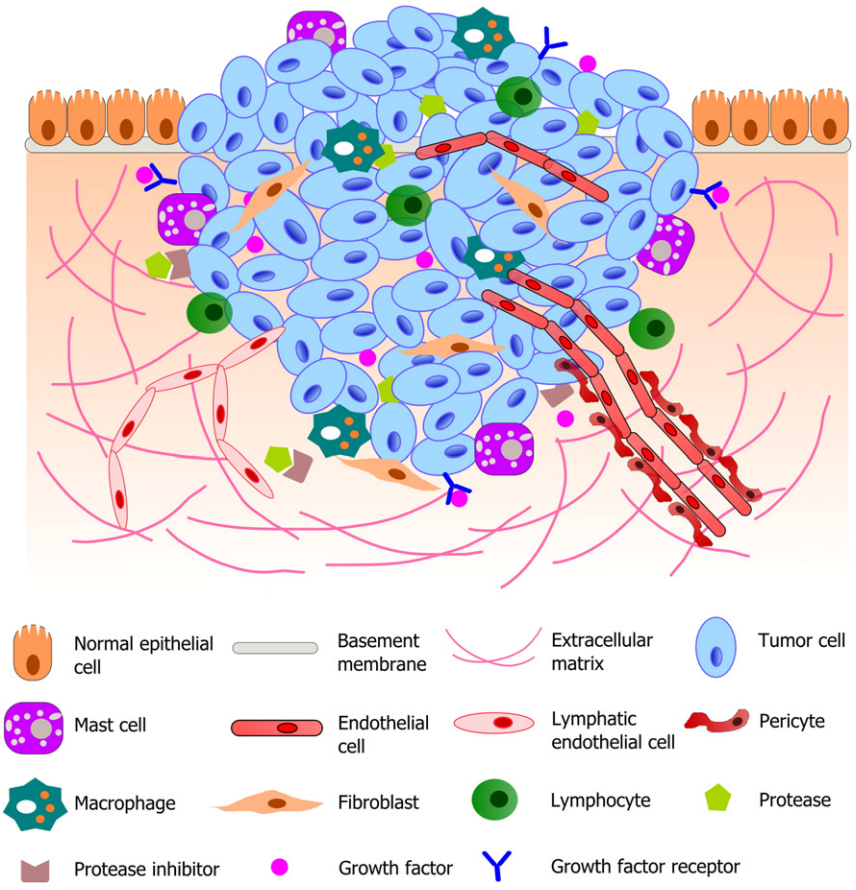

Fig. 1. Schematic illustration of a typical tumor microenvironment. Cancer cells reside in a complex microenvironment containing various supporting cells, extracellular matrix (ECM) and a suite of signaling molecules. These environmental components collectively contribute to the tumor-stromal interaction and tumor progression. Adapted from (Joyce and Pollard, 2009; Koontongkaew, 2013).