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From competency to dormancy: a 3D model to study cancer cells and drug responsiveness

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Abstract

Background: The heterogeneous and dynamic tumor microenvironment has significant impact on cancer cell proliferation, invasion, drug response, and is probably associated with entering dormancy and recurrence. However, these complex settings are hard to recapitulate in vitro.

Methods: In this study, we mimic different restriction forces that tumor cells are exposed to using a physiologically relevant 3D model with tunable mechanical stiffness.

Results: Breast cancer MDA-MB-231, colon cancer HCT-116 and pancreatic cancer CFPAC cells embedded in the stiffer gels exhibit a changed morphology and cluster formation, prolonged doubling time, and a slower metabolism rate, recapitulating the pathway from competency to dormancy. Altering environmental restriction allows them to re-enter and exit dormant conditions and change their sensitivities to drugs such as paclitaxol and gemcitabine. Cells surviving drug treatments can still regain competent growth and form tumors in vivo.

Conclusion: We have successfully developed an in vitro 3D model to mimic the effects of matrix restriction on tumor cells and this high throughput model can be used to study tumor cellular functions and their drug responses in their different states. This all in one platform may aid effective drug development.

Keywords: 3D cell culture, Microenvironment, Drug response, Dormancy, Competency

Background

Solid tumors expose cells to a heterogeneous and complex extracellular matrix environment. Tumor phenotype are highly dependent on complex interactions with the surrounding cells and the ECM [1, 2]. Tumor ECM composition, fiber orientation, patterns of infiltration and volume have been used as independent clinical prognostic indicators several cancer types [3–5]. Matrix stiffness induced by type I collagen deposition and cross-linking has been shown previously to promote malignant transformation [6, 7]. Other extracellular matrix components such as laminin, fibronectin, tenascin have been observed in breast and primary small cell lung cancers in studies associated with cancer metastasis and drug resistance [8, 9].

In addition to ECM components, cells secreted enzymes such as lysyl oxidase (LOX) and matrix metalloproteinases (MMPs) also contribute to the establishment and maintenance of the pre-metastatic niche [10, 11]. LOX released from hypoxic tumor cells at the primary site are able to induce cross-linking of collagen and further increase matrix stiffness. The increased ECM stiffness could be a body defense mechanism to shield diseased cells from uncontrollable growth. On the other hand, the expression and activity of MMPs are enhanced in almost every type of human cancer and correlate with the progression of tumor stage, occurrence of invasion and metastasis, and mortality [12, 13]. In an in vivo study, the inoculated cancer cell proliferation was decreased in tumors generated from *Mmp9*-deficient mice compared to wild-type mice [14].

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