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Editorial

Microfluidics with 3D Culture: Reconstituting Tumor Microenvironment *In Vitro*

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The microfluidic approach strives to reproduce the in vivo tumor microenvironment, enabling the study of cellular interactions within and surrounding the tumor, control of physiomechanical properties, and administration of drug treatments to determine sensitivity and response. Tumor microenvironment is important to consider in oncology research as it can preferentially influence tumor proliferation, metastasis and metabolism. It is also a critical factor in drug penetration and competence. Thorough investigation of the tumor climate will lead to potential targets for drug agents and improve earlier diagnosis and treatment of cancer. Progress using the microfluidic technique has been made, yet much still waits to be explored and understood regarding the cancer microenvironment.

Microfluidics has recently been explored as an innovative *in vitro* approach to oncology research. Its novelty lies in constructing a more predictable microenvironment, and in simulating in vivo dynamics with increased accuracy [1]. Tumor microenvironment is a heterogeneous and complex ecosystem involving different cell types and many physical and chemical cues [3]. A microfluidic chip, consisting of a network of microchannels (1 to 1000 μm) to process and manipulate small volumes of fluid [4], can precisely recapitulate one or more aspects of the cancer microenvironment, including cell-cell interaction, cell-extracellular matrix interaction, gradients of soluble factors, and interstitial flow, etc [5]. Microfluidics, when combined with 3D cell culture, can closely mimic the tumor microenvironment found in physiological settings [6]. 2D cell culture consists of a thin monolayer of cells growing on a flat, restricted, two-dimensional synthetic substrate. In contrast, 3D cell culture allows multiple layers of cells to grow and interact naturally with other cells in a three-dimensional substrate, a closer representation of the in vivo neighborhood [2]. Advantages of the microfluidic chip include its multiple channels, allowing for co-culture of tumor cells and various other stromal cells, controlled pressure gradients and flow velocities through each individual channel, and the potential to introduce hydrodynamic stress on cells along the microfluidic channels similar to that of endothelial cells lining blood vessels in vivo [2]. These important features of the microfluidic device are several critical components involved in the tumor microenvironment [3]. Investigation of multiple stimuli and properties characteristic of the tumor area defines the premise of this field of research [2].

Tumor growth involves both cell-cell communication as well as cell-matrix communication and the changes that occur by these relationships may contribute to abnormal proliferation and metastasis [2]. Microfluidics is very useful for exploring and understanding the cellular processes and physiomechanical properties of the tumor microenvironment [2]. The cellular composition of the tumor climate, includes not only tumor cells, but growth factors, fibroblasts and Cancer-associated Fibroblasts (CAFs), endothelial cells, MSCs, and inflammation cells [2]. The 3D microfluidic device is capable of co-culturing tumor cells with CAFs or with MSCs to mimic their in vivo association, model a physiologically comparable vascular network exhibiting intravasation, extravasation and tumor angiogenesis, and create variable flow and diffusion gradients to monitor response to soluble growth factors [2]. Other characteristics of the cancerous domain are the elasticity or stiffness of the matrix and hydrodynamics affecting the area [2]. Such properties of the tumor ECM are significant to consider as they contribute to the growth and migration of the tumor [2]. Interstitial flow through the ECM aids movement of growth factors and other biomolecules in the direction of the tumor environment forming a diffusion gradient [2]. The microfluidic device is capable of accurate regulation of laminar flow through each microchannel, creating similar physiological conditions affected by interstitial fluid movement [2]. Further, control of physical properties of the 3D substrate enables simulation of in vivo cell-matrix interactions [2].

Through familiarity with the biochemical and biophysical components and their regulation in the tumor area, application of the microfluidic approach can be extended to drug therapy [6]. The tumor microenvironment is a key player in drug resistance [2]. Abnormal interstitial fluid flow and aberrant growth and aggregation of cells, called spheroids, surround the tumor domain [7]. These components can decrease or entirely blockade a drug agent's penetration to targeted cells [7]. Thus, investigation of the mechanisms and regulation of the surrounding tumor environment can illuminate potential targets for anti-cancer drug therapy [3]. The 3D microfluidic approach is more representative of the physiological environment and is thus a more practical way to study drug sensitivity than 2D culture [3]. It offers multiple cell layers, hydrodynamic complexity, and the ability to control precisely the flow properties throughout the device channels

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that affect the path of the drug [3]. Microfluidics holds much promise for the future of earlier cancer diagnosis and improved drug treatments [3].

Current progress in the field of microfluidic research manifests in improving the understanding of the hydrodynamics and physiomechanical properties of the tumor microenvironment [3]. Sung and Schuler used the microfluidic approach to study the efficacy of an anti-cancer drug on colon cancer cells [8,9]. Their experiment showed that flow properties surrounding the tumor have a significant effect on successful delivery of the drug to the target area and on the cells responsiveness to the drug [8,9]. Other experiments involve regulation of flow dynamics by modeling a physiologically comparable vascular network within multiple microfluidic channels [10]. Zervantonakis et al. are still working to elucidate the effects of flow dynamics on vasculature functioning and activity within and surrounding the tumor area [10]. This proposes a promising avenue for drug therapy targeting the vascular network along with tumor cells undergoing intravasation and extravasation during metastasis. Song et al. have also performed studies designed to co-culture circulating breast tumor cells with endothelial cells and investigate how hydrodynamic stress affects tumor angiogenesis [11]. Results support shear stress as a stimulus of tumor-endothelium binding with CXCR4 expression [11]. Other experiments have been geared towards reversing the over proliferative tumor ECM to improve drug delivery and decrease the metastatic phenotype [12]. In a study by Netti et al., a treatment was applied to degrade collagen in the surrounding tumor matrix [12]. As a result, the rate of diffusion of the IgG antibody was enhanced [12]. This advocated degradation of the tumor ECM as a hopeful avenue to be explored in the future to improve drug delivery and reduce aggressive tumor migration [13]. Similar experiments to explore the physical properties of the tumor ECM have been performed by Ramanujan et al. [14]. They studied the effects of different concentrations of collagen within the 3D hydrogel, resembling in vivo matrix properties [14]. Results indicated that the collagen component of the tumor ECM is key in preventing diffusion into the tumor tissue [14]. In addition, varying the collagen properties within the 3D substrate accurately represented diffusion gradients around tumors in vivo [14]. Furthermore, microfluidics is particularly pertinent to pancreatic cancer research, as pancreatic tumor cells are outweighed by stromal cells in the surrounding area [15].Thus, tumor microenvironment is a critical consideration for the advancement of our understanding of pancreatic cancer biology and treatment response [15].

Microfluidic research is an exciting approach that promotes conditions that are physiologically consistent, such as three dimensional growth, cell-cell and cell-matrix interactions, interstitial fluid flow and diffusion gradients, and channels mimicking vasculature [3].Understanding tumor microenvironment is increasingly important in order to determine effective drug treatment strategies [2].Future application of this methodology lies in its potential for reconstituting a tumor environment more representative of the physiological environment to support the tumor cells during the drug screening process and ultimately to test the drug sensitivity for individual patients [2].

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