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Introduction

Biomedical researchers in the basic research, governmental, and clinical laboratories, as well as biotech and pharmaceutical industry have become increasingly aware of the limitations of time-honored conventional 2-D tissue cell cultures where most tissue cell studies have been carried out. They are now searching and embracing 3-D cell culture systems, something between a Petri dish and a mouse. It becomes apparent that 3-D cell culture offers a more realistic micro- and local environment, where the functional properties of cells can be observed and manipulated that are not possible in animals. The important implications of 3-D tissue cell cultures for basic cell biology, tumor biology, high-content drug screening, and regenerative medicine and beyond are far-reaching.

In this special topic series, these researchers address the urgent need to further advance the concept of 3-D tissue cell culture, especially relevant for cancer and tumor cell culture studies. To transform the conventional 2-D cell cultures into 3-D cell culture systems requires two key aspects. First, it requires a conceptual change not only to think differently, to ask big questions, but also not to be afraid to be ridiculed, paper rejected and grants turned down at times. Second, 3-D tissue cell cultures also require development of new materials, new tools, and new imaging capability. With the advent of development of confocal, two-photon, and multi-photon imaging systems, as well as other imaging reagents, it is now possible to capture stunning 3-D images that reveal a wealth of previously missed information. Equally important is the development of new designer materials, new nanofiber scaffolds, and other biological matrices. The combination and complementary new tools now usher a new era of 3-D cell culture that will enrich our knowledge about cells. It will not be surprising if in the decades ahead, the 3-D cell culture will become conventional, and along with it, much information about how cells truly behave will be learned.

In this collection of papers, these authors present their long-held view that 2-D cultures cannot address the 3-D microenvironment in bodies. These authors include the leading proponents of 3-D tissue cell cultures over the decades. Mina Bissell, a long-time champion of the 3-D tissue cell culture from her experience of studying breast cancer, elegantly summarized the dynamic reciprocity—engineering 3-D culture models of breast architecture, function, morphogenesis, tissue structure, and neoplastic transformation. Hynda Kleinman and George Martin not only describe the history of discovery and development of the Matrigel system with their colleagues over 20 years ago, but also its wide use in a variety of cell cultures and other areas today. Edna Cukierman and Dorothy Beacham summarize 3-D cell culture systems that mimic the in vivo microenvironment. They suggest that these systems provide unique experimental tools to identify early alterations in stromagenesis that are supportive of tumor progression with the ultimate goal of blocking neoplastic permissiveness and restoring normal phenotypes. Leland Chung and co-workers describe 3-D co-culture models to study prostate cancer growth, progression, and metastasis in bones. Kim describes the development of more complex heterologous 3-D tumor microenvironment and tumor spheroid models that can be used to address a number of questions. Ingemar Ernberg and co-workers summarize their finding, using both experiments and bioinformatics for the growing concerns about the reality of 2-D cell culture and argue for 3-D cultures. They also discuss how cells grown in 3-D cultures may have more physiological interactions with neighbouring cells and extracellular matrix.

It is known that most deadly cancers undergo metastasis that eventually becomes untreatable in patients. Thus, it is crucial to fully understand how a variety of cancer cells migrate. Currently, most cancer cell migration studies in literature have been on 2-D solid surface even if they are coated with soft substrata, but they do not reflect the reality in the body. Cells in the body always migrate in a 3-D space. Thomas Dittmar and co-workers have developed a 3-D extravasation model that can be used for selection of highly motile and metastatic cancer cells and also an assay that is a valuable tool for the identification of genes, which are the key players at switchboards of the intracellular signaling pathways. Frank Entschladen and co-workers summarize their in vitro and in vivo imaging of cell migrations, two important complementary methods to unravel metastasis formation.

In my laboratory, we have developed a new class of chemically synthetic designer self-assembling peptide nanofiber scaffolds that may be used for a variety of cell cultures

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including cancer and tumor cells. These peptides are short with very high purity, every single component is known. They can not only be designed, redesigned, modified readily at single amino acid level to incorporate a wide range of known biologically active peptide motifs, but can also be scaled up at a reasonable cost for widespread use. Researchers are likely to find diverse uses in this new class of designer nanofiber peptide scaffolds with custom-desired functionality.

I believe it is time to move away from 2-D tissue cell culture technology that predates the last century. Quantitative biology requires in vitro culture systems that more authentically represent a cell's environment in a living organism. In doing so, in vitro experimentation can truly become more predictive of in vivo systems.

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