3D tumor spheroids

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Abstract

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Introduction

PDAC belongs to the top five of cancer-related deaths in the world and the poor prognosis is primarily due to its advanced stage at diagnosis , the progress in its treatment remains too slow as a consequence of the complex physiopathology of this tumor characterized by a heterogeneous cellular composition and the accumulation of a very dense fibrotic tissue [**???**]: Due to that pancreatic cancer is a heterogeneous disease, is often modelled using established cell lines in the laboratory.

In recent years, three-dimensional (3D) culture systems have gained increasing recognition as an effective tool for biological research. One widely used 3D culturing technique is the application of multicellular spheroids (MCS).Cells cultured in 3D more closely mimic the physiological environment compared to conventional monolayer culture systems. Spheroids are three-dimensional spherical cellular aggregates with high cell-density, that more closely simulate conditions existing in solid tumors where hypoxia and alterations related to intracellular metabolism occur due to poor availability of nutrients from blood vessels [2].

Pancreatic tumor microenvironment

In Pancreatic ductal adenocarcinoma (PDAC), the major components of the tumor microenvironment are a complex population of fibroblasts forming the bulk of the stroma, vasculature, inflammatory and immune cells [3]. PDAC is associated with evolving alterations in the tumor microenvironment, including increasing fibrosis and extracellular matrix deposition (desmoplasia). Increasing desmoplasia accompanies progressive disease and creates intratumoral pressure that compresses the vasculature, resulting in limited blood flow to the tumor and consequent hypoxia and low nutrient delivery [4].

2D and 3D cell culture

Cell culture is a widely used *in vitro* tool to improve the understanding of cell biology, cellular mechanisms, tissue morphology, drug action, protein production and the development of tissue engineering [5].

Three-dimensional (3D) cell culture is well documented to regain intrinsic metabolic properties and to better mimic the in vivo situation than two-dimensional (2D) cell culture [6].

A comparative molecular analyses from 2D and 3D *in vitro* conditions revealed that cancer cell phenotype is highly influenced by its microenvironment.Through the examination of cancer cell transcriptional behavior, cellular processes were closely linked to functions promoted by different culturing conditions. Cancer cells grown in monolayers favored rapid proliferation, and this behavior was corroborated by up-regulation of cell cycle progression genes in addition to metabolic processes that synthesize DNA, RNA, and proteins. Unlike cancer cells cultured in monolayers, cancer cells in 3D down-regulate proliferative processes, while up-regulating genes involved in ECM organization and cell adhesion [7].

When performing 3D cell culture experiments, the cell environment can be manipulated to mimic that of a cell in vivo and provide more accurate data about cell-to-cell interactions, tumor characteristics, drug discovery, metabolic profiling, stem cell research, and other types of diseases [8].

Alterations in cancer cell behavior under different growth conditions underlie the importance of defining culturing conditions that preserve endogenous tumor behavior. While monolayer cultures promote the most non-native behavior of cancer cells, this model still maintains value due to its ease and scalability towards applications targeting cancer-growth driving pathways. However, analysis and discovery of potential therapeutics targeting stromal interactions, ECM development, or cell signaling may yield erroneous results in this system.The 3D culturing and inclusion of stromal cell types do show increased similarity to in vivo cancer behavior. However, improvements upon ex vivo culture conditions that allow all stromal components to persist will greatly enhance our ability to conduct pre-clinical screens that may more closely recapitulate the biological responses of patients [7].

The structure of multicellular spheroids.

Methods for the generation of MCS

MCS and PDA

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