

3D tumor spheroids

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Abstract

Open collaborative writing with Manubot [1](#)

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 (PDA), 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](#). PDA 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](#).

Interactions between the neoplastic and non-neoplastic cells and cellular matrix have been proposed to stimulate the extensive desmoplastic reaction. Stroma production is promoted by the activation of multiple cell signalling pathways [[5](#); 10.1002/mc.20827] these signalling cascades lead to secretion of structural matrix components including proteoglycans, collagen and fibronectin and the activation of catalytic enzymes such as proteinases.

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases, they are involved in degradation of the extracellular matrix. MMPs support tissue remodeling and stimulate neovascularization and inflammatory response, both in physiological and in pathological conditions, for example, in tumors [6](#).

MMP-2, MMP-7, and MMP-9 expressions correlate with various morphological features of the PDAC tumor such as inflammation, necrosis, and formation of the new blood vessels [7](#) and their tissue inhibitors (TIMPs) TIMPs 1–3 compared with normal pancreas [8](#).

Pancreatic stellate cells (PSC) are responsible for desmoplastic generation [9](#). The activation of PSC from a quiescent to an activated state is an intercellular stimuli from tumor-stromal interactions. PSCs can be transformed into myofibroblast-like cells, which express α -smooth muscle actin (α -SMA) as cancer-associated fibroblasts (CAF) [[10](#); 10.1053/j.gastro.2010.05.084].

CAF are important components of tumor stroma and affect cancer growth, survival, metastasis, angiogenesis and resistance to chemotherapy or radiotherapy through various cytokines [11](#), and contribute to a diminished immune function [12](#).

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 [13](#).

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 [14](#).

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 [15](#).

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 [16](#).

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 [15](#).

The structure of multicellular spheroids.

MCSs are cell aggregates with complex cell-to-cell adhesions and cell-to-matrix interactions, which results in gradient generation for nutrients, gases, growth factors and signal factors [17](#).

It has been reported that MCS formation involves three critical steps. In the first stage, dispersed single-cells are drawn closer to form aggregations where ECM fibers act as a long-chain linker through the binding of integrins. This is followed by a period in which cell aggregates pause in compaction, because of the accumulation of sufficient amounts of E-cadherins. Finally, in the third stage, cells are compacted into solid aggregates to form MCSs due to the homophilic cadherin-cadherin binding [18](#).

The formation of MCS process initiates with an spontaneous self-assembly and cell-cell interactions. These interactions are regulated by adhesions proteins such as E-cadherin, α -catenin and P-cadherin [[19](#); doi.org/10.1038/s41598-018-19384-0; 10.3892/ijo.31.6.1403] Cell-to-matrix interactions is the base for cell building and is influenced by integrins mainly by β 1-integrin. The integration of integrin-

ECM facilitates the cell aggregation process that connect a cell with its environment in the context of spheroid formation [[18](#); 10.1016/S0002-9440(10)63058-1; 10.1007/s00441-005-0148-2].

The cytoskeleton also plays an important role in spheroid formation. During spheroid formation the actin filaments undergo significant changes and the expanded microfilaments as stress fibres become along the cell periphery. In this step, the cytoskeleton is a force generation structure performing a continuous pre-stressed lattice that keeps structural stability [[20](#); 10.1002/1097-0169(200103)48:3<175::AID-CM1007>3.0.CO;2-2].

The internal structure of spheroids comprises different cell layers. MCS include hypoxic, proliferative apoptotic/necrotic areas as a consequence of oxygen and nutrient gradients [???]. Small micro-spheroids of <200µm diameter mostly include proliferating and normoxic cells, mimic three-dimensional cell-cell and cell-matrix interactions but they are inappropriate to reflect pathophysiological conditions with hypoxic areas in the spheroid center or to mimic proliferation gradients [21](#). However, spheroids with diameters of approximately 200-300µm results in a typical zonation, with proliferative zones at the surface co-existing with normoxic quiescent zones in the middle and hypoxic zones in the core [22](#). Finally, MCS > 500 µm diameter the formation of necrotic areas is observed as described in microregion of tumor *in vivo* [23](#).

Due to these characteristics, MCS mimic the first avascular stages of tumor formation, and exhibit important tumor aggressiveness features such as enhanced multicellular resistance, migration, and invasion, as well as an enhanced clonogenic capacity [24](#).

Methods for the generation of MCS

MCS and PDA

Due to that pancreatic cancer is a heterogeneous disease researchers have been developed models capable to reproduce *in vitro* the heterogeneous tumor microenvironment.

Several methods to create 3D tumors *in vitro* have been proposed, with hanging drop technique being the simplest and most frequently used. However, in many cell lines this method has failed to form the desired 3D tumor structures.

A modified hanging drop method for 3D spheroid formation facilitated with methylcellulose yield a straightforward production of spheroids in PDAC cells and form well-rounded spheroids after 5 days in hanging drops. These spheroids have high tolerance to mechanical force, thus enabling standard manipulations and display some hallmarks of solid tumors, such as hypoxic zone, proliferating cells, and apoptotic regions [25](#).

3D pancreatic cancer spheroids, based on pancreatic cancer cells and fibroblast co-culture demonstrate innate desmoplastic properties and stay poorly permeable with relevant diffusion barrier function. Spheroid-based xenografts produced different extracellular matrix (ECM) components with uniformity in terms of ECM architecture recapitulating clinical PDAC tumors. Moreover, establishment of tumors by transplantation of spheroids demonstrate higher expression of pro-fibrotic and pro-survival PDAC hallmarks [26](#).

In the last years the characterization of a novel 3D tumor model has been in full swing. A triple co-culture of pancreatic cancer cells (PANC-1), fibroblasts (MRC-5) and endothelial cells (HUVEC) to form a heterotype multicellular tumor spheroid (MCTS). The integration of the three cell types enable the presence of a core rich in fibroblasts and fibronectin in which endothelial cells are homogeneously distributed [27](#).

A microchannel model allow to develop a 3D pancreatic tumor in *vitro* by co-culturing pancreatic tumor spheroids with PSC in a collagen matrix. Under these conditions spheroids and PSCs are mutually activated when co-cultured. Under co-culture condition, tumor spheroids acquire a migratory phenotype with cancer cell-cell interactions, cell-ECM interactions, and cancer cell-PSC interactions [28](#).

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