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Primary Bone Tumors and its Advancement into 3D

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Abstract

Primary bone tumors, such as osteosarcoma, are highly aggressive pediatric tumors that develop lung metastases in 30% of cases and are characterized by a poor prognosis. Bone is also the third most common metastatic site in patients with advanced cancer, and when tumor cells settle in the skeleton, the disease is usually considered incurable and treatment is palliative. Osteosarcoma and bone metastases share a niche with the microenvironment of the same tissue. 3D culture is a new and promising approach for studying the interaction of tumor cells with other cells or cell-free components of the tumor microenvironment (fibroblasts, mesenchymal stem cells, bone ECM, etc.). In fact, 3D models can mimic the physiological interactions that are important for regulating soluble paraclinic factor response, tumor drug resistance, and aggression, and overall, these innovative models are animal-based. It may be possible to avoid the use of preclinical cancer models. So far, static and dynamic 3D cell culture models have proven to be particularly suitable for screening anticancer agents, providing accurate information by transforming in vitro cell cultures into precision medicine. This short report summarizes the latest technologies in the field of primary and metastatic bone tumors, the various methods and techniques used to realize 3D cell culture systems, and the path to personalized medicine.

Keywords: Bone tumors; Microenvironment; Fibroblasts; Cell culture

Introduction

Osteosarcoma is a mesenchymal disease. They are derived from bone, and mesenchymal stem cells (MSCs) are tumor-forming progenitor cells [1, 2] and are also stromal cells [3, 4] involved in tumor development. In bone, tumor-supporting stroma is formed by osteoblasts (bone-forming cells derived from MSC), osteolytic cells (bone-absorbing cells), endothelial and immune cells, and MSC. Osteoclasts attach to the bone surface and the range of factors involved in their activation may depend on the type of tumor. For example, osteoclasts can be stimulated directly by tumor cells [5, 6] or by tumor-induced osteoblasts [7]. In OS, the presence of osteoclasts in the tumor microenvironment may promote the behavior of osteoblasts in tumor cells and increase their aggression [8] and is considered a poor prognosis factor [9]. Similarly, in BM, a delicate balance between bone deposition and resorption forms a pathogenic process [10]. Given the complexity and heterogeneity of bone tumors, treatment strategies aimed at eradicating them show a consistent slowdown compared to many other carcinomas. A better understanding of osteosarcoma carcinogenesis is clearly needed to overcome drug resistance and improve low survival. Many disorders make it difficult to study bone cancer with current tools. These are effective for the physical difficulty of manipulating bone as tissue, the rarity of sarcoma tumors, the difficulty of obtaining tumor tissue fragments from human patients with BM, and human disease includes a limited number of models to mimic. For all these reasons, the need for a new cell model of osteosarcoma is becoming increasingly important. This review focused on cellular models currently available for BM or sarcoma research. There have been recent advances from 2D to 3D cell culture models to model multicellular systems. Three-dimensional architecture is one of the main themes based on the formation of tissues and organs. This complexity begins during embryogenesis and is increased by cell-cell contact, which is the basis of intracellular function [11]. In addition, the cells are surrounded by ECM. It is important in determining cell differentiation, proliferation and homeostasis [12]. Therefore, an ideal 3D culture model should not only properly mimic carcinogenesis and maintenance of tumor cell proliferation, but also mimic the interactions between mixed cells within the ECM. To date, several techniques have been developed and explored for this purpose. 3D static cultures include seeding of cells with a spherical structure that does not contain extracellular matrix, and seeding of cells into a matrix or scaffold made of natural or synthetic biomaterial. 3D dynamic cultures include bioreactor-cultured spheroids or scaffolds and cell dissemination on microfluidic perfusion devices.

Spheroids

One of the pioneering studies that opened the field of 3D culture is Sutherland et al. It is a study of [13]; they found that floating and proliferated lung cells were in the outer zone of proliferating cells, the malnourished and oxygenated intermediate zone with few mitotic cells, and the central zone of necrosis, which is a physiological feature. We first observed the formation of developing spheroids. Tumor mass forced levitation spheroids are the easiest way to generate spheroids. It prevents cells from adhering to the bottom of the well and provides buoyant aggregates and cell-cell contact. The hanging drop method is the most widely used and static technique [14]. Conversely, rotating cell culture bioreactors, spinner flasks, or agitated tank cultures [15] force uniform spheroid formation by continuous agitation [16]. Again, spheroids can be formed by a single cell type or mimic the interactions between multiple cells. B. Tumors and stromal cells [17]. These culture systems are highly reproducible and have low manufacturing costs. As early as 1971, it was clear that spheroids could be used for drug screening and radiation therapy testing [18] despite the benefits, not all cell lines form spheroids, and some just form unpredictable cell aggregates.

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Matrices and Scaffolds

Similar to spheroids, cells seeded in a matrix or scaffold can be cultured in either static or dynamic culture using a rotating cell culture bioreactor. A hydrogel-based matrix is a network of hydrophilic, physically or chemically cross-linked polymer molecules that retain large amounts of water [19] and provide a 3D biomimetic environment that supports cell proliferation and differentiation. Masu [20] the great advantage of hydrogels is that they adapt to the specific properties of ECM. For example, hydrogels can be designed to contract or swell based on the environmental stimuli they receive [19] and can be easily concentrated with specific cell adhesion ligands to mimic soft tissue. Hydrogels are synthetic or naturally derived [21] and are primarily based on matrigel, collagen, or fibrin. Matrigel is derived from mouse sarcoma and has the most heterogeneous composition. The main components are structural proteins such as laminin, nidgen, collagen, and heparan sulfate proteoglycan. Matrigel polymerization is temperature dependent. Collagen-based hydrogels are also pH-dependent and play an important role in cancer progression and are the most abundant protein in mammalian ECM. However, due to pH dependence, collagen-based hydrogels are unsuitable for studying the effects of tumor acidosis, a key feature in the development of bone cancer [22,23] or cancer-induced bone pain [24,25] will be 3D scaffolds, traditionally described as tools made from polymer biomaterials, provide attachment sites and hydrogel-like interstitial spaces for cells to grow and proliferate, thereby forming 3D structures. This has the advantage of providing a reproduction of the ECM [16]. Scaffold stiffness can be adjusted to affect cell adhesion, proliferation, and activation [26]. The materials used for scaffolding are biocompatible and must induce molecular biometric recognition of cells [27]. Biomaterials that mimic ECM are considered to be the most biocompatible, consisting of collagen, hyaluronic acid, matrigel, elastin, laminin-rich extracellular matrix, and alginate, chitosan, and silk. Synthetic biomaterials include two-phase systems such as polyethylene glycol, hyaluronic acid-PEG, polyvinyl alcohol, polycaprolactone, or polyethylene glycol-dextran. Many biomaterials, such as ceramics, can fall into the categories of natural or synthetic materials [28].

Microfluidic Device

Recent advances in tissue engineering have led to the development of living multicellular microculture systems that are maintained in a controllable microenvironment and function at organ-level complexity [29]. Applications of these "on-chip" technologies are becoming more and more popular in cancer research [30]. The importance of these systems is that continuous perfusion of the medium through the microfluidic network can mimic blood flow and exchange nutrients, oxygen, and metabolites that are important for modeling living cancerous tissue with blood tissue innovation [31]. Invading cells that detach from solid tumors are exposed to the new microenvironment of the circulatory system. Depending on the size of the blood vessel, blood flow velocity can reach 0.03-40 cm / s, arterial hemodynamic shear force is 4.0-30.0 dyne / cm^2, and venous shear force is 0.5-4.0 dyne / cm^2 [32].

Therefore, tumor cells need to adapt rapidly from static growth to fluid shear stress. This is a condition that static culture cannot handle. Until a few years ago, microdisks only supported 2D environments. Recently, 3D was introduced to support 3D aggregates. Finally, microfluidics have enabled the design and development of self-organized organ-like cell aggregates derived from the pluripotent stem cells organoids, opening up a whole new level of biomimetics. Typical examples are the blood-brain barrier, 3D neural network, kidney, liver, or intact intestinal epithelium, or glioma, breast cancer, or sarcoma model when it comes to cancerous tissue [30]. This technique has the ability to add multiple cell lines on the same chip. It is possible to mimic the interactions between tumors and endothelial cells that are the basis of the metastatic process, including, for example, angiogenesis, intravascular invasion, and colonization of cancer cells. Similarly, microfluidics has been thoroughly studied to better reproduce the interactions between cancer cells and immune cells, with the ultimate goal of expanding knowledge of cancer immunotherapy. Finally, the formation of 3D spheroids has been combined using hanging drops on a microfluidic platform for drug testing or chemical reaction assays. The next big challenge is to fully validate these models before implementing them in the pharmaceutical industry's drug development pipeline and ultimately in personalized medicine applications.

Conclusion

Three-dimensional models have the potential to identify key molecular signaling pathways and establish a robust preclinical platform for assessing the clinical efficacy of new drugs that inhibit the development and progression of cancer.

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Conflict of Interest

There are no conflict of interest.

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