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Predication on organs-on-chips applications the systematic treatment of breast cancer

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Abstract. With the continuous development of cancer therapy, traditional in vitro models have been unable to reproduce the structure of organs and tissues of various parts of the human body, fluid flow and mechanical stimulation characteristics, and the human tumor microenvironment, which is crucial to the study of the behavior and progress of cancer, can not be presented through the animal model in vivo, which shows that the traditional physiological model of cancer can no longer meet the research of human anti-cancer therapy. Benefits from the continuous infusion of cell cultures through the microchannel, the device of organ-on-a-chip improves cell viability and activity and facilitates the simulation of the tumor cell microenvironment, which is expected to further replace traditional zoological experiments. This study reviews a method to simulate the microenvironment of the vitro breast cancer metastasis combined with microfluidic technology, and the application of this device in relevant researches of breast cancer cell metastasis and screening of breast cancer therapeutics.

Keywords: Organ-on-a-chip, Breast cancer, Cancer metastasis, Drug testing

1. Introduction

As one of the most familiar cancer types, breast cancer mainly occurs in women, which causes numerous women's deaths in the world per year. IARC (International Agency for Research on Cancer) shows from the latest global cancer incidence data that breast cancer surpassed lung cancer for the first time to become the top cancer in the world, and the amount of new cases of breast cancer worldwide reached 2.26 million in 2020, which shows breast cancer becomes a potential threat for women[1]. The uncontrolled proliferation of mammary epithelial cells under the action of various carcinogenic factors is the cause of breast cancer. Breast cancer occurs mainly in women and is often referred to as the "pink killer." [2].

In 2016, on the World Economic Forum's list, human organ-on-a-chip technology was one of the "top ten emerging technologies." Organ-on-a-chip is a revolutionary method that could one day replace animal testing [3]. The organ chip provides a highly bionic breast organ unit. Compared with traditional animal experiments, the microfluidic system has high data acquisition efficiency and can better simulate the actual situation of human organs. It has the advantages of strong replication, avoiding human interference, saving economic costs, and so on. Besides, organ-on-a-chip can detect the dynamic, spread, and metabolic activities of tumor cells in human functional tissues and organ environments in vitro, which plays an important role in drug toxicity analysis, tumor modeling, and

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drug metabolism. [4]. This paper reviews the in vitro culture of breast cancer cells based on organ chips, commonly used in vitro models of breast cancer cell metastasis, and several basic medicine tests.

2. In Vitro Culture of Breast Cancer Cells

Two-dimensional cell culture plays a crucial part in cancer research, but it has a good deal of limitations because it cannot simulate the microenvironment of the original tumor and cannot accurately represent tissue cells in vitro. For example, because the cell can only grow and expand in two dimensions, the cell is slender and flat and cannot be preserved in its natural form [5]. In addition, there are some differences in cell differentiation, drug metabolism and gene expression. Three-dimensional cell culture overcomes some of the limitations of traditional two-dimensional cell culture, reducing the differences in drug screening between in vitro and in vivo models and reducing the possibility of using animal models for experiments. But they were unable to reproduce the chemical and physical characteristics of the tumor microenvironment, lacking the fluid flow, tissue deformation, and shear stress that play important roles in cancer cell invasion. Animal models are ethically controversial, expensive, and do not predict the actual effects of drugs on humans [6].

System-on-a-chip is a convenient and versatile approach that can be applied to simulating the functions of various organs in the human body, enabling the implantation of human cells, creating patients's specific multicellular settings for conducting personalized medical research, and providing a platform for studying the interaction of actual organs with proposed therapies. In recent years, the in vitro culture of breast cancer cells based on organ chips has been successfully put into experiments and made relevant progress.

The researchers cultured human breast cancer cells with a combination of immortalized human breast fibroblasts and a variety of extracellular matrix factors in a microfluidic device [7]. The results showed that human breast fibroblasts promoted the growth of breast cell clusters compared to monocultures, especially in the presence of an extracellular environment rich in fibronectin. Factors that influence tumor growth also include changes in the levels of cytokines secreted by adjacent normal parenchymal cells in the local tissue microenvironment.

3. In Vitro Model Construction of Breast Cancer Cell Metastasis

Tumor metastasis is a multi-step complex process, which refers to the process in which cancer cells transfer from the original tumor site to distant tissues and organs to form other tumor sites. Almost 90% of cancer patients die due to tumor spread[1]. Breast cancer cells metastasis is strongly linked to the primary microenvironment and other tumor positions, and sufficient interaction between the microenvironment and tumor cells is crucial for whether tumor cells can survival. However, the common two-dimensional tumor model cannot accurately and intuitively reflect the three-dimensional structure of the tumor inside the human body, how the tumor cells interact with each other, and the related mechanisms of life activities such as cell genetics and metabolism in tumor microenvironment. Therefore, the multi-organ interaction and real-time monitoring of dynamic, functional and physiological responses of living organs are realized by using organ chips.

3.1. Metastasis Mechanism of Breast Cancer Cells

Tumor cells initiate the metastasis cascade by interacting with other organ microenvironments at the cell-to-cell and cell-to-extracellular matrix levels. The metastatic cascade, which means to spread tumor cells from the original tumor position to other distant organs, is a dynamic and intricate process. The occurrence of metastasis begins when the cancer cells begin to migrate to the surrounding matrix. Then they enter the vascular system and metastasize to other organs to form secondary tumors. Some cancer cells attach to the vessel walls after entering the vessel circulation and exude into the new microenvironment of the target organ. Cancer cells adjust and eventually form new tumors in the tissue environment at the secondary site. The metastasis of breast cancer is closely related to its subtype.

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The types of Breast cancer include luminal A, luminal B, triple-negative, and HER2-positive types, and the classification of breast cancer is relevant to hormone receptors and cells. When using organ-chip to study breast cancer metastasis, liver, lung, brain and bone are considered as potential metastatic sites, among which luminal A and luminal B tend to metastasize to bone, HER2-enriched breast cancer mainly leads to liver metastasis, while TNBC subtype has a higher tendency to lung metastasis [8].

Bersini's team created a three-dimensional microfluidic model to analyze bone metastasis specificity in human breast cancer [9]. Through this system, the extracellular matrix of proteins secreted by bone-differentiated cells can better simulate the complex signals in the cellular microenvironment, generating the microenvironment of muscle and acellular collage. Due to the components secreted in the bone microenvironment that promote the exosmosis of breast cancer cells, tumor cells can specifically move toward the bone. These results suggest that tumor cells have a tendency to seek an acceptable microenvironment to maintain proliferative growth and the process of tumor metastasis. Through the construction of an organ-on-chips model, the human tumor microenvironment is better simulated, which is conducive to the study of the metastasis mechanism of the tumor cell microenvironment.

3.2. Common In Vitro Construction Models based on Organ Chips

In addition to studying how breast cancer cells metastasis, organ chips can also simulate the process of breast cancer cells invade to other organs and cells[10]. In one study, the researchers simulated the invasion of breast cancer under the action of macrophages. A three-dimensional breast cancer in vitro invasion model was created by using microfluidic system. Prepare two channels, fill them with 3D matrix gel before placing the tubes in parallel. Macrophages stained with red fluorescent protein and tumor cells stained with green fluorescent protein were implanted separately. Put HUVECs suspensions in nutrient supply channels to form a single permeable vascular endothelial barrier to simulate blood vessels of mammals. The total migration distance can be determined by connecting the channels between macrophages and tumor cells through the gaps between microchannels and calculating the number of tumors migrating to adjacent channels. The system mimics the arrangement of microorgans in the body, recreating a more biomimetic external environment. There is also a 3D model consists of a cell-filled hydrogel, creating an endoderm model of breast cancer cells by replicates tumor cells stroma and blood vessel networks. The model shows that breast cancer cells exhibit different aggressiveness depending on their ability to metastasize and whether a vascular layer presence or not.

The organs-on-chips model can simulate the coordination and internal connection of multiple organs as well. Nowadays, researchers have already achieved long-term co-culture of skin, intestinal, liver, kidney and other organoids on a chip, and establish a multi-organ chip with the combination of various organs [11]. Besides, the combination of chip and multi-mode sensing technology is the future development trend to realize the information acquisition and processing of multi-organ chip. A multi-organ chip, with integrated electrochemical and immune sensing modules, can synchronously monitor cell microenvironment parameters such as carbon dioxide concentration, power of hydrogen and temperature, as well as some biomarkers that reflect tissue function.

4. Drug Testing and Analysis of Breast Cancer Cell Prevention and Treatment based on Cell Chip

In traditional drug testing, due to the complexity and heterogeneity of tumors, patients often have different therapeutic effects under the same drug treatment, so it is difficult to determine the best treatment plan for each patient. By reconstructing the genetic and genetic signatures of the primary tumor, organ chips have great potential for medicine response testing in several given cancer subtypes with unique genome mutations. Moreover, through the construction of multi-organ chips, the metabolism and influence of drugs can be better observed, and the possible side effects of drugs can be screened for patients.

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In one study, triple-negative breast cancer cells were exposed to a series of anticancer drugs (olaparib, fir, cisplatin, etc.) to characterize the inoculation density, ECM composition and biochemical conditions, based on an organ-on-a-chip platform for the testing of breast cancer treatment methods [12]. The results showed that the response of organ-on-a-chip model cell lines to cisplatin was more similar to physiological response. Therefore, this technology is a promising individualized medical tool, which is conducive to patients to choose the appropriate treatment method. In the process of drug development, organ chips can also be used to achieve the screening of different concentrations of drugs, greatly saving screening time. Eduati's team created a microfluidic platform that can quickly examine a variety of medicine combinations in cell analysis[13]. On this platform, Braille valve chip was mounted the on the Braille display, using an internal bracket to press the dimethylsiloxane chip onto the Braille pin. A program designed according to a predefined sequence corresponding to the system's drug binding and barcode controls the movement of each Braille pin. By adding organoids from pancreatic tumors to the system, 62 conditions generated in turn were used to test the overall efficacy of each drug under all combinations. Using this device, the effectiveness of single sensitive medicine or multi-medicine combination chemotherapy regimen can be effectively detected, and the efficiency of drug detection can be greatly improved. Compared with the traditional model, this method can detect different drugs quickly and accurately at the same time, and multiple gradient tests can also be conducted to determine the concentration of anticancer drugs, which can improve the efficiency of future cancer drug research and development.

This paper argues that drug testing on an organ-on-a-chip should be accompanied by an evaluation of drug absorption, distribution, metabolism, excretion, and toxicity of chemotherapy, immunotherapy drugs, or radiation. If necessary, multiple organ functions can be reconstructed on the chip platform, so that the multiple organs and tissues that need to be observed are connected together, and the metabolic network similar to that of individual or combination medicine in human bodies can be built. The construction of in vitro models of multiple organ connections can provide a better understanding of drug properties, better potential side effects and prediction of efficacy in new drugs and treatment events, and provide a precious integration of regenerative medicine and translational science.

5. Conclusion

Through the process of breast cancer cells cultured in vitro, a highly bionic breast organ chip is constructed, which can better simulate the human tumor microenvironment and realize further research on the metastasis mechanism and invasion process of breast cancer cells. At the same time, organ chip also greatly improves the screening of different drugs and drug concentrations for breast cancer treatment, and simulates the metabolic process of drugs through multi-organ chip to detect the possible side effects of drugs on patients to the greatest extent. The shortcoming of this paper is that it only reviews the treatment method and diagnosis of breast cancer, which has not been integrated with the research on organ chips such as lung cancer and liver cancer, and the number of review articles is limited. Nowadays, there are still many deficiencies in the field of multi-organ chip, there is no clear distinction between the concept of organ chip and organoid chip, and the standards for drug testing on organ chip are not perfect. With the gradual maturity and specification of organ-on-chip technology standards, it will have further comprehensive applications in precision medicine and biodefense strategies.

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