Stem cell and organoid modeling in cancer study

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Abstract. Stem cells are of many types and play important roles in the development and repair of tissue. The first time when we discovered the stem cell, different types of stem cells were brought into our vision—such as embryonic stem cells; and somatic stem cells. Stem cell therapy is rising rapidly these days and has become an important treatment in the medical system. They have been tried to apply in different kinds of disease treatments such as cancer, nerve injury, ocular diseases, etc. But besides these, there are some other special stem cells such as cancer stem cells (CSCs). CSCs are the cells that drive the growth of the tumor and often depend on the tumor microenvironment. When they are combined with 3D printing technology and organ transplantation, they can do more things like simulating the organ's environment figuring out how the disease and drugs work, and making the product of the stem cell therapy apply in the human body. And the combination of stem cell therapy and 3D printing technology is a rising way for us to study and treat this disease. However, some difficulties and hurdles are still on the road to development, we still need to focus on how to make them fully functional in the human body and the issue of medical ethics.

Keywords: Stem cell, Cancer stem cell, Tumor microenvironment, 3D printing, Heterogeneous.

1. Introduction

1.1. What is a stem cell, characteristics and functions of stem cells

Stem cells are some kinds of unique cells that can differentiate from other different kinds of heterogeneous stem cells, and some other special types like cancer stem cells. Their functions are similar in general and each one may have some other unique functions. The somatic stem cells can form various tissues and organs and repair the damaged cells and parts of our bodies [1]. Some such as cancer stem cells are important tools and methods for the treatment of cancer. The main characteristic of stem cells is that they can self-renewal and replicate and produce certain tissues or organisms, even a living body if the stem cell is totipotent [2]. Somatic stem cells are abundant in human bodies, especially in the early stages of human development. Some somatic stem cells such as hemopoietic stem cells are well-known and essential for the human body. But CSCs are not very traditional stem cells for us. It is like some cell subpopulation, which has the same characteristics as the stem cells in the tumor tissues and organs [3]. The CSC model is like a dynamic cell population with the function of cancer cells rather than a stable cell population with the responsibility of regenerating the tumor [4]. The cancer stem cell was first identified from solid cancers and some hypotheses have been talked about more and more and with increasing interest. The CSC concept was first formulated in the 19th century and in 1961 researchers proposed that cancer and tumors are the sick and abnormal conditions of the normal cells and will cause the continuous and unstoppable growth of the tissues [5]. However, the researchers still took almost 100 years to validate the nowadays cancer cell hypothesis. And finally, after 10 years, the CSCs were truly identified in the solid cancers [6]. According to the recent CSC hypothesis, the CSC population is responsible for the initial cancer, it could start the tumors and create and increase the heterogeneous cell populations. Some organs are identified to be the place where CSCs likely to grow. The brain and breast are popular for CSCs and melanoma has also been found these years [7] more evidence says that CSCs will affect the therapy by resisting and transferring leading to the death of the patients [8]. In general, the main functions and characteristics of CSCs are self-renewal, replication, the initiation to induce the tumor, and the long potential repopulation. For example, the mouse is going to have tumors if around 3 AML CSCs were injected into its body and the initial formation of tumors is going to have a thirty-to-one-hundred-fold expansion up to 8 weeks [9].

1.2. What is the principle of the therapy of using CSCs

The therapy we use most these days is chemotherapy, but the chemotherapeutic and bio-imaging reagents that are specific for the CSCs are limited because of some same properties as other cells [10]. More and more evidence show that CSC theory is a crucial mechanism in whether we can completely eradicate cancer [11]. So, some new therapy based on the interaction between CSCs and CSCs enabling microenvironment comes up. CSCs can reconstruct tumors with aggressive and other malignant biological behaviors by self-renewal and infinite proliferation. Located in the cancer niches, one feature is its cellular plasticity [12]. The special interaction between tumor cells and their microenvironment is the essential point for CSCs to reproduce and survive. The CSCs also seem to adjust their metabolism by acquiring the intermediate metabolic types to adapt to the changes in the microenvironment [13]. Therefore, the therapy of cancer can be based on targeting the synergistic interaction between CSCs and CSCs enabling a microenvironment that can prevent the CSCs and the tumors from surviving. For treating solid cancers, we can use some specific signatures of cell surface proteins to identify them. However, this method is not very developed for many tumors. Some research points out that the close relationship between CSCs and their microenvironment creates the place for CSCs to grow and CSCs can easily self-renewal and replicate to form the different cell layers of the solid cancers. The detailed principles may be a little complicated. Between the CSCs and their environment, there are lots of complex intercellular signaling networks, and the signaling pathways construct the way to cell stemness, plasticity, and metastasis as well [14]. By adjusting the pathways that are defective in CSCs, we can affect the outcomes of the therapy [15]. Also, the relationship and interaction in some tumors can be bidirectional, which means that while the molecules and elements in the microenvironment will affect the functions and behaviors of CSCs, the CSCs can somehow change the environment at the same time as well. The phenomenon may be clear in the brain cancers that were shown in the former research. It has shown that the CSCs are preferred the high concentrations of oxygen and are more likely to exist in the perivascular niches that are relatively well-oxygenated. Something interesting is that the endothelial cells will produce certain ligands to cause and promote the tumors. Therefore, we can use this feature to treat the cancer by interrupting the balanced microenvironment or creating some target site for our drugs that are used against the cancer. Some research also shows that the condition of CSCs may not be a cell-autonomous process, but determined by the tumor microenvironment. Research about the secretome of melanoma cells entering senescence after chemotherapy-induced CSC phenotype in non-stem melanoma cells also confirmed that the differentiation of the cancer tissues is directed. So, these researches proved and supported that the cancer stem cells are regulated tightly by the tumor microenvironment. For example, researchers target some surface-specific markers like Notch and Hedgehog in breast CSCs to try to enhance CSC apoptosis and treat it [16]. By designing a treatment that will focus on the microenvironment of the tumors and affect the functions of the CSCs, we should understand the reasons that cause the CSCs and increase the possibility for us to treat them with better results.

2. Obtain better CSC models by using 3D printing technology

Due to the small number of CSCs in the cancer tissue that we cannot investigate directly, we can achieve CSCs from induced pluripotent stem cells (iPSCs) using conditioned media during cancer cell culture. Because of the significant limitations in simulating the natural environment, we can use 3D printing to gain new types of cell culture such as the culture containing lung cells and CSCs, or use the 3D printing to establish the glioma stem cell model from the modified porous gelatin, alginate, and fibrinogen hydrogel [17]. Such as the method of using 3D printing to produce lung cancer stem cells, gives us a good idea to use some new ways to study the CSCs culture model system and achieve better CSCs and models for future study and treatment [18]. The novel in vitro lung CSC culture models and systems will be developed by using 3D printing technology and it can be a new method for us to study the characteristics of CSCs. Using 3D printing technology includes several aspects. First is the construction of the 3D scaffolds. Some common materials we use today are ABS (Filament Direct), HIPS (Gizmodorks), and PLA (Filament Direct). These three are all polymers we use to produce the rigid structure. 10% GelMA and 15% PEGDA may also be used in the scaffolds through printing [19]. Then a certain computer model can be designed with several relevant dimensions if needed. The advantage of using these materials is that they will form small channels and pores, which makes it easy for us to control spatial distribution and increase the stability of the rigid structure. Some good mechanical features can also be performed in these materials. When we focus on the characterization of 3D scaffolds, one way is that we can use the scanning electron microscope. It can perform the image of the scaffold samples. The establishment and maintenance of the cell cultures are also important. To establish 3D cultures, we can make the cells trypsinized first and seed the cells with the density the experiment required on the 3D printed scaffold matrices. Then we can seed the cell lines in different kinds of plates based on the experiments. Then we can do the viability and proliferation, we can also stain the cells if we need to. The reagents needed are variable and depend on the experiment. The general idea is to use the buffer to wash the samples and dry them for the next imagining step. For example, to stain, we can use the Texas Red-X phalloidin and 4′,6-di-amino-2-phenylindole (DAPI) in the lung cancer stem cell system. Compared to the normal rigid scaffolds, on the GelMA-PEGDA scaffolds cell cultures showed more significant changes and the morphological differences are more noticeable. The results may be variable because of the different scaffolds and the degree of proliferation may also be different due to the different kinds of cells. By using this model, it can provide an effective way to study the cancer such as applying in studying the ovarian cancer stem cells (OV-CSCs) with the hierarchical model and intend to prolong the lifetime of the patients [20].

3. Hurdles in CSC treatment, development, and application

The cancer or intratumor heterogeneity is a challenge for cancer treatment [21]. We still need to develop a deeper understanding of heterogeneity and better models of how CSCs and non-stem cancer cells interrelate [22]. And the understanding of the distinct mechanism of tumor stem cells and their regulatory pathways is still not cleared and required development [23]. Despite that, we also need new and advanced technologies in 3D printing and organ transplantation to create a novel alternative tool to study cancer. Although we know a lot about many aspects of CSCs the gap is still huge in not only its complete relationship with its microenvironment but also in the improvement of the environment modeling and 3D system construction. In recent experiments and studies, researchers are still used to use the 2D cell cultures to experiment and they rely on it much more than the 3D printing technology. The disadvantage of this is that sometimes researchers may not detect the components in the microenvironment and fail in some drug developments [24]. Therefore, spreading the technology to more researchers and letting them trust and accept it at the same time is also crucial to the development and application. Another barrier or challenge is that some supportive cells of the true environment may not exist in the 3D cultures which means that the model is not very similar to the real condition. Besides this, the matrix composition sometimes also has differences from the real condition, so the heterogeneous component is another point for the treatment and development. The models today can’t fit the heterogeneous components very well and it will be a progress if the future development of the model should be more accommodating to the heterogeneous components of the tumor. For example, we can use some specialized scaffolds to co-culture both the patient’s cancer and the stromal cells. Such methods and actions will expand our insight into CSC biology and provide more unique and novel opinions and treatments for the researchers to develop specific therapies.

4. Conclusion

With the statements above, cancer stem cells are common in the medical field, and treating cancer is an important goal for researchers to study and achieve. Starting with the basic functions and characteristics of the CSCs, we can learn about the CSCs in different aspects and know the principles behind them. Then considering it with its microenvironment can let us know the CSCs more comprehensively and can finally invent some novel methods or tools to treat it. Combined with the 3D printing technology, we can simulate the condition of the disease that approach the real one and acquire the data and the results more directly and professionally. However, some barriers and challenges still exist. The more detailed principles and interactions are not very clear. The technology is not very developed yet and it is not popularized well in the research areas. Thus, it is still a long road for us to treat cancer very well, but focusing on these problems and insisting on this area will provide crucial insight for the CSCs and develop efficient specific therapies for the CSCs treatment.

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