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Review Article

Dig the root of cancer: targeting cancer stem cells therapy

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Cancer stem cells are a subpopulation of cancer cells which have stem cell characteristics and play vital role in tumor formation, metastasis, relapse and resistance to chemo- drugs. Exploring drugs or designing novel approaches to target cancer stem cells will contribute greatly to cancer therapy. The first step of exploring effective drugs to cancer stem cells is to acquire cancer stem cells and characterize their properties. Developing the targeting drugs could be based on the characteristics of cancer stem cells, like signal pathways contributing to self-renew, ability to pump small molecules out and quiescence. This review will summarizing the current approaches of designing drugs to target cancer stem cells.

Keywords: cancer stem cells, self-renew, targeting therapy

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Introduction

Cancer is a severe disease leading to millions of death in the worldwide [1, 2] and it is now first cause of death. The most used methods for cancer treatment are surgery, chemo-therapy and radio-therapy. However, most cancers resist to these treatment and relapse after long time treatment. In the recent years, researchers found that there are a subpopulation of cells, playing like stem cells of cancer. As they highly express stemness genes, keep the self-renew ability and are able to differentiate to other non-stemness cancer cells, they are termed as cancer stem cells (CSCs). They stay in quiescent status and resist to traditional chemo-therapy and radio-therapy. Although there is a stochastic model with opinion that all the subpopulation of tumor cells can generate a tumor. However, more and more studies demonstrated recently that the hierarchy model. Only a subpopulation of tumor cells, named cancer stem cell or cancer initiating cells, but the other populations can generate a tumor (Fig. 1) [3].

Researchers isolated CSCs from patients' tissues and cancer cell lines in different types of cancers, including breast cancer, brain cancer, leukemia, liver cancer, colon cancer and others[4-9]. They are mostly isolated based on the cell surface markers, like CD44+CD24- in breast cancer, CD133+ in brain cancer and CD34+CD38- in Leukemia[8, 10, 9]. Culturing as spheroid bodies in serum-free medium with growth factors and isolating side populations are also used to obtain CSCs[11, 12, 6, 13].

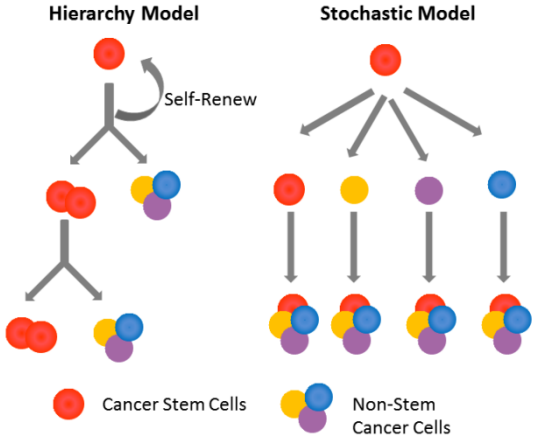

Figure 1. Hierarchy model and Stochastic model

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CSCs is the root of cancer. Traditional methods can kill non-stem cancer cells, but not CSCs. The tumors shrink in the short time. However, the remaining CSCs can proliferate, differentiate and generate a relapsed tumor. If the developed drugs can target CSCs, the root of the cancer is eliminated. The tumor lost its ability of self-renew. It will shrink in the long time. If these two types of treatments are combined, both the non-stem cancer cells and CSCs will be eliminated. The tumors will be able to cured (Fig. 2).

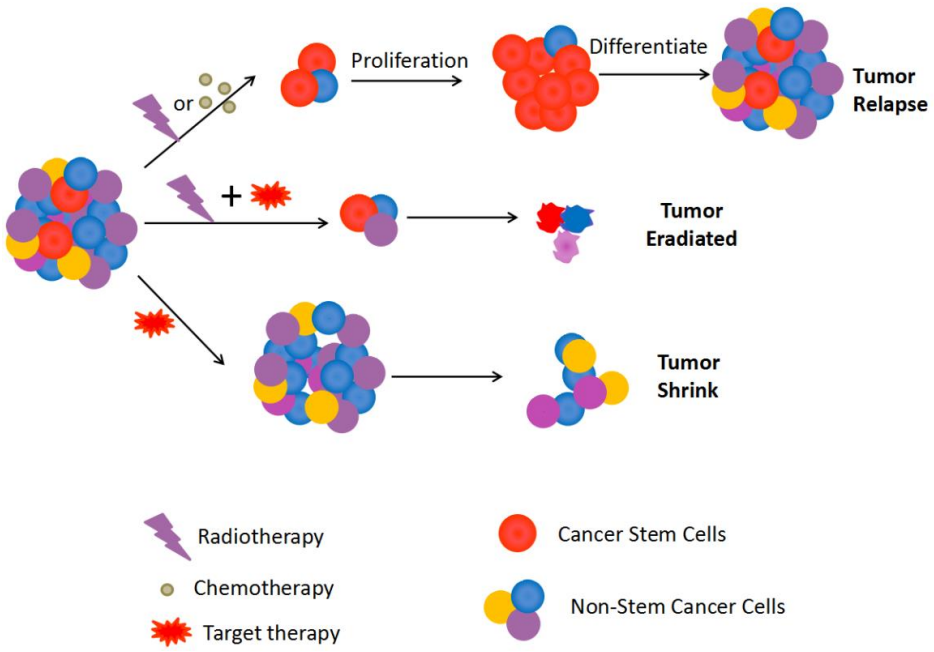

Figure 2. Cancer stem cells model

Treatment by targeting cancer stem cells

As the traditional cancer therapeutic methods hardly show any effects on cancer stem cells, developing new drugs that targeting to cancer stem cells is vital for cancer therapy. There are many ways to explore the effective drugs targeting to cancer stem cells, such as by screening on active drugs already exists or untested drugs with potential activity, self-renew pathways targeting, destroy the cancer micro-environments and oncolytic viruses treatment (Fig. 3).

High throughput drug screening

High throughput drug screening contributes to find out the specific molecule that most effectively target key signal pathways of cancer stem cells. Then the influence of it to cell morphology and signal pathway of cancer stem cells would be further characterized to determine the effect of the drug. In chronic lymphocytic leukemia, research by high throughput drug screening found that the small molecule Salinomycin could inhibit leukemia through inhibition to Wnt pathway [14]. Besides, researches showed that Salinomycin also exhibited inhibitory effect on other types of cancer stem cells [15]. The small molecules screen on cancer stem cells showed that serotonin and monoamine signal pathways are potential targets of brain cancer therapy [16]. Additional, RNAi pool screening also could be a method to seek effective cancer stem cell targets, thus could cure cancer stem cells by RNA interference or small molecules designed. In brain cancer, TRRAP was explored by RNAi screening which was quantified to related with cell proliferation and self-renew and TRRAP interference could infect tumor formation[17].

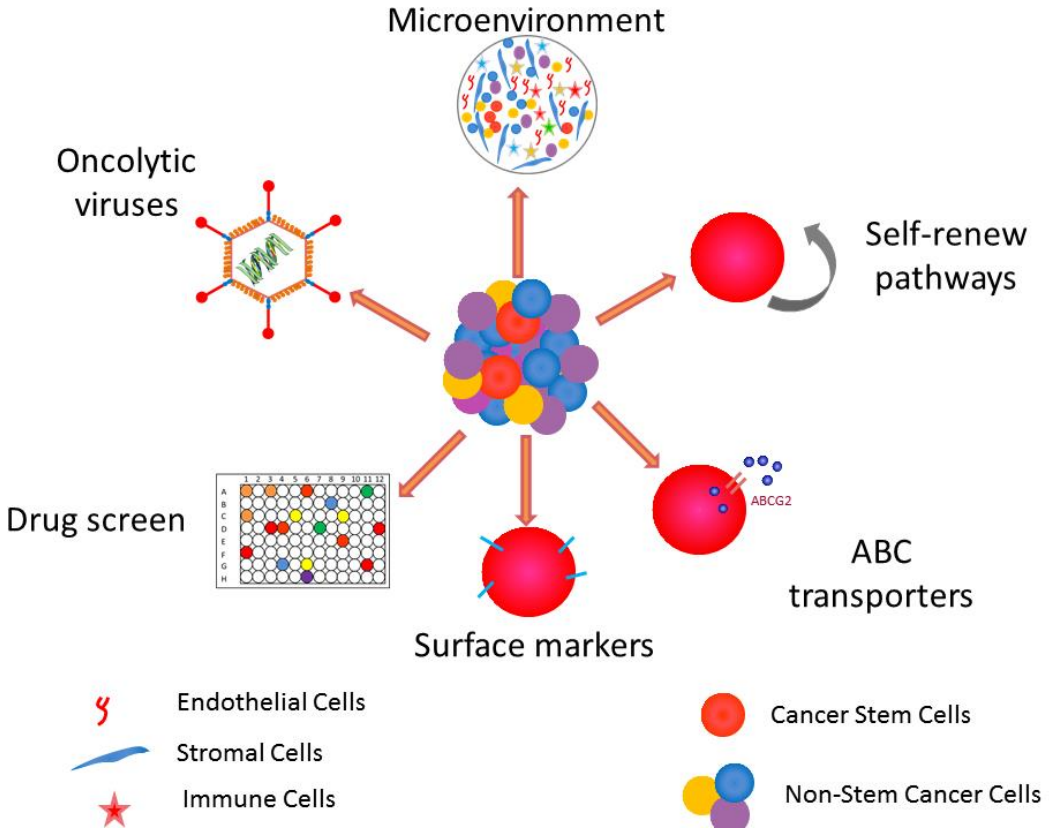

Figure 3. Approaches in targeting cancer stem cells.

Inhibition of self-renew signal pathway

Signals such as Notch and Hedgehog are intensely related to the self-renewal ability of cancer stem cells. The r-secretase inhibitor of Notch pathway GSIs could prevent cleavage of r-secretase and keeping it to cell membrane thus inhibit Notch signal pathway. Inhibition of Notch signal pathway could inhibit cell proliferation and promote cell differentiation[18-21]. Besides, inhibition of Hedgehog signal pathway could also inhibit tumor effectively, having promised effect in clinic[22]. PTEN/AKT signal pathway also important to cancer stem cells and disable of PTEN activity could activate AKT thus induce activation of Wnt signal pathway which not only have great influence on tumor cell and stem cell, but also on cancer stem cell[14, 23, 24]. Wnt signal pathway is also an important part of cancer stem cells thus high throughput screening of small molecules targeting to Wnt also has great anti-cancer stem cell effect such as Salinomycin on chronic lymphoma leukemia in clinic [14].

Cancer micro-environment

The micro-environment is critical to cancer progression. The immune cells, endothelial cells and stroma cells exhibit different roles in maintaining the cancer. They plays very important role in CSCs maintenance as well. Notch pathway in endothelial cells significant promote the stemness of brain CSCs[18, 20]. Developing the drugs targeting the micro-environment of CSCs will eliminate CSCs, the root of cancer.

Surface marker and ABC transports targeting

Cancer stem cells have high expressed ABC family proteins which help them to pump small molecules out of cells. Besides, they are always in quiescent status thus insensitive to chemical drugs. Additional, cancer stem cells have higher expression of anti-apoptosis proteins such as Bcl-2, XIAP and survivin and stronger DNA repair ability than non-cancer stem cells[25-27]. So cancer stem cells often resistant to chemical drugs and radio-therapy. The cancer stem cell theory proposed recent years considered that cancer therapy killed only non-cancer stem cells could shrink tumor in short period while tumor would relapse after a time due to differentiation and proliferation of

cancer stem cells, but on the other hand, if targeting to cancer stem cells and killing them directly, tumor would shrink and disappear due to shortage of self-renewal cancer stem cells even though the therapy hadn't effect on tumor cells. So it is meaningful to develop drugs targeting to cancer stem cells to promote cancer therapy.

Resistance to anti-apoptosis molecules

High expression of anti-apoptosis molecules is one of the main reason that contributes to resistance of cancer stem cells to traditional therapeutic drugs. The molecules of IAP families such as XIAP and survivin have high expression in cancer stem cells, thus employ them with strong anti-drugs ability[28, 25, 26]. Besides, other anti-apoptosis proteins such as Bcl-2 also play functions on drug resistance.

Oncolytic Virus therapy

Cancer stem cells could pump small molecules out of cells with the help of ABC family proteins on their cell membrane thus show out as insensitive to drugs when treated with small molecule drugs. While virus is a kind of active particle which always connects with receptors of cell membrane through its surface molecules then enters cells in certain way and toxic to tumor cells. Virus has many advantages in cancer stem cell therapy. Firstly, The ABC families of cancer stem cell membranes couldn't pump virus out[29, 12, 6]. Secondly, some viruses such as adenovirus could infect not only active cells but also the cells in quiescent status such as cancer stem cells[11]. Thirdly, viruses replicate and package themselves in cells and ultimately lyse cells thus cancer stem cells, even though have high level of anti-apoptosis proteins and damage repairing system which render them ability of resistant to small molecule drugs, couldn't resistant to viruses[30].

Virus is an effective way of treating cancer stem cells. They could be as a vector in non-replicate form and armed with genes or shRNAs targeting to key signal pathway of cancer stem cells or armed with a killing gene to inhibit cancer stem cells[31, 32]. Besides, the oncolytic viruses which only replicate themselves in tumor cells could also armed with killing genes thus have both killing cell and lyse cell ability to enforce the effect of them on cancer stem cells[11].

Oncolytic viruses could specific replicate in tumor cells thus has little side effect. Besides, they could infect and lyse cancer stem cells directly due to characteristics of themselves. So oncolytic virus is a good way targeting to cancer stem cells. In present, many oncolytic viruses have been used for cancer therapy including DNA viruses such as adenovirus, poxviruses, herpes viruses and RNA viruses such as retroviruses[33-38]. Each virus has its own advantages and disadvantages and has important role in cancer therapy, besides they could kill cancer stem cells as well. The targeting therapeutic effect of different viruses on cancer stem cells would be detailed as followers.

Conclusion

Cancer stem cells were the main obstacles of traditional cancer therapeutic methods. High throughput screening could help to explore drugs specific targeting to cancer stem cells, besides, molecules designed targeting to key signal pathways of cancer stem cells could also help to overcome the obstacles of resistance to drugs. Virus therapy has many advantages compared with small molecule drugs, such as viruses couldn't be pumped out by cancer stem cells, don't easy induce resistance to them and have effect on even cells in quiescent status, while combined viruses with gene such as oncolytic adenoviruses armed with genes targeting to self-renewal related pathways of cancer stem cells had better effect on cancer therapy. So to eliminate the origin of tumor cells radically by combination of many methods targeting to cancer stem cells could bring great effect on cancer therapy.

Competing interests

The authors declare that they have no competing interests.

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None

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