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Editorial

Novel Function of Old Drugs in Targeting Cancer Stem Cells

Haineng Xu*

Department of Radiation Oncology, University of Pennsylvania Perelman School of Medicine, Philadelphia, USA

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***Corresponding author**

Haineng Xu, Department of Radiation Oncology, University of Pennsylvania School of Medicine, Philadelphia, USA, Email(s): xuhaineng123@163.com (or) Haineng.Xu@uphs.upenn.edu

Editorial

Cancer is a severe disease and growing as the leading cause of disease induced death. It leads to 8.2 million death in 2012 and got 14.2 million cases. This is an enormous burden to the patients, their families and the whole society. Currently the major ways for cancer therapy are mostly three traditional methods: surgery, chemotherapy and radiotherapy [1]. In the recent years, with the developing of biochemical researches, some bio-therapeutic methods were applied on cancer therapy. Immunotherapy [2], receptor kinase targeting therapy [3] and gene therapy [4] were developed. These novel approaches and their combination with the traditional methods dramatically improved the efficiency in some types of cancers. However, some cancer cells may relapse after treatment and some cancer cells may resist to chemo- or radio-therapies. Also, some cancers have already metastasized at the time of diagnosis. Due to these issues, it is still a big challenge in developing more efficient drugs to eliminate cancers.

In 1994, Lapidot, T, et al. found that the CD34+CD38- cells in leukemia could engraft SCID mice to generate amount of colony-forming progenitors. However, the other cells populations didn't possess this property [1]. Al-Hajj, M, et al. reported in 2003 that the CD24- cells could produce tumors much stronger than the CD24+ cells [5]. There were amount of subsequently reports on the similar phenomenon in various cancers. A specific small subpopulation plays greater roles than other cells in cancer. They called these as cancer-initiating cells or Cancer Stem Cells (CSCs). As the developing of this field, researchers find that the CSCs are critical for cancer progression, chemo- or radio- resistance, cancer relapse and metastasis. They are responsible for the renew and are considered as the root of the cancer. For the traditional methods, the bulk cancer cells are killed but not the CSCs as its quiescent status. The tumors shrink in a short time during the treatment. However, after the treatment, some CSCs will release from its quiescent status, proliferate and differentiate into bulk cancer cells. Also, some CSCs will keep their renewal property. These make the cancer relapse in a long time after treatment. If we utilize CSCs targeting drugs to treat cancers, the renewal property of cancers will be prohibited. The tumors will shrink in a long time [6].

Due to the critical role of CSCs in cancer therapy, multiple approaches are introduced to target cancer stem cells. As the cancer stem cells are able to pump the chemo-drugs out of cells through their surface ATP binding cassette transporter, cancer stem cells are resistant to chemo-therapy. Oncolytic viruses could replicate in CSCs, unable to be pumped out and directly lyzed the CSCs [7,8]. Researchers also designed shRNAs or inhibitors to target the self-renewal associated pathway, like Wnt [9], Notch [10] and Hedgehog [11], to block the self-renew of CSCs. Besides these specific designed approaches, people use unbiased drug screen to search efficient drug in targeting CSCs as well [12,13].

For searching efficient drugs in targeting CSCs, researchers used unidentified drug pool or FDA approved drugs to treat CSCs. The effect of the small molecules on the cell viability or stemness on CSCs will be evaluated. One or several putative efficient drugs will be selected for further confirmation. In 2012, Sachlos, E, et al. used compound libraries to screen drugs on the neoplastic and normal human Pluripotent Stem Cells (hPSC). The cell viability and differentiation were both considered for drug selection. The authors found an interesting drug, thoridazine, an antipsychotic drug. It was also demonstrated with inhbitory effect on leukemia and breast CSCs in this paper. Thoridazine is an inhibitor of dopamine receptor D2 family proteins [13]. It has already been approved by FDA and classically used to treat patients with psychotic problems.

The novel function of the old drug attracted lots of attentions. People found inhibitory ability of thioridazine on cancer cells or CSCs in various types of cancers, gastric cancer, cervical cancer, liver cancer, glioblastoma, endometrial cancer and ovarian cancer. Thioridazine could induce CSCs apoptosis and inhibit cell viability in vitro. It also prevented tumor growth *in vivo*. Thioridazine regulates the key pathways, FAK-mTOR [14], PI3K/Akt/mTOR, to alter cells viability *in vitro* and *in vivo* [15]. Thioridazine was also wrapped into nanomaterial to target CSCs [16]. Besides the effect of thoridazine, the expression of dopamine receptors and their correlation with cancer prognosis

were analyzed. These further support the function of thoridazine in targeting CSCs.

In the Cell paper, Sachlos, E. et al. found the novel anti-CSCs function of an old antipsychotic drug thioridazine. Its effect was further confirmed by other researchers in the various kinds of cancers. As thioridazine is a FDA approved drug, it will easily be used for clinical research on cancer by targeting CSCs. This is a big advantage in comparison with new developed drugs. Its application in cancer therapy will be largely shortened.

Besides thioridazine, some other small molecules were also discovered through screening. In 2009, by high-throughput screen, Gupta PB disclosed that salinomycin reduced the CSCs population over 100 fold than paclitaxel, a commonly used chemotherapeutic drug for breast cancer [12]. Salinomycin could inhibit CSCs self-renew by inhibiting Wnt signaling and selectively induced cancer cells apoptosis [9]. Its anti-CSCs effect was demonstrated in some other cancers as well, like gastric CSCs and lung CSCs. In 2014, Jiang, et al. discovered the anti-tumor function of pitavastatin, a drug regulating blood cholesterol, in glioblastoma through drug screen in NIH clinical collection compounds. Subsequently research found that pitavastatin could inhibitor glioblastoma stem cells [17,18]. Anti-protozoal drug emetine [19], anthelmintic drug Niclosamide [20] and some other drugs were discovered with novel function in targeting cancer or CSCs.

As the critical role of CSCs in various cancers, developing efficient approaches to target CSCs is important in cancer therapy. Developing specific oncolytic viruses to lyze the CSCs, inhibiting CSCs self-renew by targeting key pathways or discovering effective drug through unbiased drug screen are three major ways of getting drugs to target CSCs. Discovering novel function of FDA approved old drug will shorten its application on clinic as its safety has already been demonstrated. More researches need to do this to search novel effective drugs or further demonstrate the current putative efficient drugs.

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