As cancer stem cells (CSCs) have been successfully isolated from tumor tissue, and CSC theories have been proposed, CSC theories supply new ideas for cancer research. CSCs have a small population in tumor tissue and have stem cell characteristics: the capacity for self-renewal and non-directional differentiation potential. CSCs may lead to tumorigenesis. CSCs are considered to be the points of origin of tumor formation and proliferation.

Significance of CSC theory in cancer therapy

Although the research history is not long, as a new area derived from stem cell research, CSCs theory has rapidly developed and has shown good prospects. CSCs have been recognized as the basis for tumor formation, growth and metastasis.

The purpose of current cancer therapy is to kill as many tumor cells as possible. Each tumor cell is believed to have unlimited proliferative capabilities, so if the tumor volume reduces, the treatment is considered as effective. However, most tumors relapse after a period of remission. According to CSC theory, traditional treatments have not completely killed the CSCs, so CSCs still proliferate unconstrained. More and more researchers point out that cancer therapy should be aimed at CSCs, which means that although tumor volume does not reduce, the proliferative ability of other cells are limited, so the tumor will gradually degenerate and shrink, perhaps finally curing the tumor[7].

Relationship between CSCs and stem cells

CSCs are only small parts of tumor cells, but they have the capacity of self-renewal and their proliferation forms the same tumor as the parental tumor. According to CSC theory, if CSCs are not eliminated, they may lead to treatment failure. Although the tumor volume may shrink significantly after treatment, relapse and distant metastasis are not prevented[2]. At present, there are two hypotheses for the origin of CSCs. One states that CSCs come from mutation accumulation or differentiated barriers of normal stem cells; the other states that CSCs originate from already differentiated primary cells or differentiated cells that dedifferentiate[3]. CSCs have been shown to generate multidrug resistance through many mechanisms, as normal stem cells[4]. CSCs may be the reason for tumor relapse after chemotherapy and radiotherapy. Reversing the drug resistance in tumors is an important direction for cancer therapy in the future.

Similarities between stem cells and CSCs

With continuous in-depth study, CSCs have been shown to share many properties of normal stem cells. First, both have the capacity of self-renewal and non-directional differentiation potential. The key difference here is that the proliferation of stem cells is self-stabilizing: when the body is in a steady state, one stem cell produces one daughter stem cell and one differentiated...
Transformation from a normal cell to a tumor cell needs a change, which generates after many stages or repeated hits. Where stem cells are the targets of mutation, they derive from mutations of normal stem cells and progenitor cells, proliferation, causing heterogeneous groups of tumor cells. CSCs and their abnormal differentiation happens during CSC differentiation processes of normal stem cells. Third, tumor cells do not divide and proliferate while in the quiescent state, thus CSCs will not be sensitive to anticancer drugs and radiation. Cuan et al. [10] used [3H] TdR infiltration to show that all CSCs were in a quiescent state, causing CSCs to not be sensitive to radiotherapy.

**Mechanisms of CSC drug resistance**

**CSCs are usually relatively static and dormant**

Cell cycle specific agents are only sensitive to certain phases of the cell proliferation cycle, and not sensitive to the G0 phase, such as the antimetabolism drug fluorouracil, anti-S phase drugs Ara-c and hydroxyurea, and the anti-M phase drug vincristine. CSCs are often in a quiescent state. CSCs do not divide and proliferate while in the quiescent state, thus CSCs will be not sensitive to anticancer drugs and radiation. According to the mechanisms of MDR, MDR is divided into natural and acquired resistance. Natural resistance means quiescent CSCs with DNA self-repair capacities and APC transporter proteins acquired drug resistance naturally. Acquired resistance means that after extended exposure to radiation or anticancer drugs, CSCs and their daughter cells display new drug resistances through the same mechanisms of accumulating mutations as normal stem cells. CSCs and their daughter cells can also accumulate MDR cells after chemotherapy as in patients with tumor relapse.

MDR1 is located on chromosome 7 at q21.1 with a total size of 330 kilobases (kb). A 170-kDa P-gp involves 1280 amino acids and comprises a similar part, which is connected by two single polypeptide chains, each part consisting of six transmembrane helices and an ATP-binding domain.
Three-dimensional structural analysis shows that if the substrate of the transporter proteins, such as anticancer drugs bound to transmembrane domains, two ATP-binding sites of the drug pump close to each other and bind with ATP, then the conformation of P-gp changes, forming channels in the middle part to directly pump out the neutral or cationic hydrophobic drugs. The structure of the MRP subfamily is similar to P-gp; its specific transport substrate is a chemotherapy drug that conjugated to combine with reduced glutathione (GST), such as etoposide, daunomycin, cisplatin, mitoxantrone, and so on. Because these substrates can pump out cells, they are also called GS-X pumps. Breast cancer resistance protein (BCRP) is a phosphorylated protein and belongs to half-transporter proteins that only have six α helices and an ATP-binding site. BCRP plays a role in homodimer formation on membranes.

**Drug pump functions of ABC transporter proteins**

ATP-binding cassette (ABC) transporter proteins are a class of transmembrane protein, and an important member of the medium-chain dehydrogenases/reductases (MDR) family. They are widely distributed in the body and can generate transit peptides, endogenous lipids, nucleotides, metabolic drugs, and enzymes. Currently, ABC transporter proteins related to drug resistance mainly involve P-glycoprotein (P-gp/ABCB1), MDR-associated protein (MRP/ABCC1), and breast cancer resistance protein (BCRP/ABCG2), which are encoded by ABCC1 and ABCG2, respectively.

**Apoptotic inhibition**

Inducing apoptosis is the common mechanism of many chemotherapy drugs. Once apoptosis is inhibited, that may lead to drug resistance of tumor cells. Genes that participate in apoptosis, such as Bcl-2, nuclear transporter xB (NF-xB), mutated p53, and c-myc, have been shown to be involved in drug resistance of tumor cells.

Mammalian cells contain at least 15 members of Bcl-2 gene family. According to their regulatory roles in apoptosis, they are divided into anti-apoptotic genes (such as Bcl-2, Bcl-x, Bcl-w, Mcl-1, AL/Bf-1, and so on) and pro-apoptotic genes (Bax, Bcl-xs, Bad, Bak, Bid, and so on). The Bcl-2 family can both suppress and promote cell apoptosis, whose biologic effects depend on the interaction among the members. Eisele et al. found that in 14 patients with de novo AML, 7 patients achieved complete remission (CR), while 7 patients showed blast persistence (BP) after treatment with cytosine arabinoside and anthracyclines. Gene expression analysis showed significant differences between the CR and BP groups with regard to apoptosis-related factors (BAX, BCL-2A1, BNIP3L, and so on) and BP samples had a 2-fold higher expression of CD34 than CR samples, indicating that LSC cells were resistant to chemotherapy through the overexpression of anti-apoptotic genes and the low expression of pro-apoptotic genes for drug resistance.

Many classic cancer-related signaling pathways have been shown to also regulate normal stem cell development. For example, overexpression of oncogene bcl-2 in the hematopoietic stem cells of mice by transgenic technology significantly increases the number of hematopoietic stem cells and enhances the capacity for resistance to lethal radiation dose tolerance in hematopoietic stem cells.

**Increasing the DNA repair capacity**

DNA is the target for most anticancer drugs and radiotherapy, such as alkylating agents and platinum compounds. In tumor cells, DNA damage will effect DNA replication and transcription directly and, in severe cases, induce cell death. However, there are anti-DNA damage repair mechanisms in tumor cells, which are primarily completed by endonuclease, DNA polymerase, and DNA ligase. The capacity for DNA replication will enhance when protein synthesis of these enzymes increases. Highly efficient DNA repair of CSCs is the most important mechanism in the resistance to chemotherapy and radiotherapy. Currently, more than 130 DNA repair related genes have been found. Therefore, the activity of DNA repair related enzymes increases. Bao et al. found that the increased capacity for DNA damage repair may be an important reason for chemotherapy and radiotherapy in CSCs.

**CSCs located in hypoxic niches**

Stem-cell niches are special microenvironments, supplying all signals for stem cell growth, transformation, and the maintenance of self-stability. CSCs are usually located in hypoxic niches, which are surrounded by differentiated tumor cells, myofibroblasts, endothelial progenitor cells, and the extracellular matrix in the microenvironment. A three-dimensional niche structure and a developed extracellular matrix may serve as a barrier to protect CSCs, keeping CSCs away from chemotherapy drugs and improving their ability to escape. In addition, DNA damage induced by radiation requires oxygen and CSCs located in a hypoxic niche are not affected by radiotherapy. The key point for CSC theory is that changes in cell microenvironments are the main reasons for delays in stem cell differentiation.

A large number of in vitro experiments show that hypoxia increases the expression of MDR1, telomerase, and CXCR, to enhance tumor drug resistance, invasion, decrease apoptosis, inhibit DNA repair, and promote tumor initiation and development. In conclusion, drug resistance of CSCs is caused by multiple factors and there are many strategies for overcoming CSC drug resistance. The drug resistance mechanism of every solid tumor is different, and therapy strategies should be different too. During chemotherapy and radiotherapy for patients with cancer, the drug resistance mechanism of each type of CSC should be considered and new factors related to tumor drug resistance should be found, thereby, using the most effective therapy to improve the effects of chemotherapy and radiotherapy, enhance patient quality-of-life, and prolong survival time.

**Prospects**

According to CSC theory, we will completely cure cancer as long as we kill CSCs. However, there are many questions to be resolved. CSCs must be separated and identified. Whether CSCs exist in each type of tumor, what the differences between gene expression are, and whether CSCs are the usual mechanisms of tumor initiation, all must be considered. Under the present conditions, the biologic characteristics of CSCs cannot be
described without effective stem cell surface markers and tracing methods. Many ideas have been based on the analysis of the phenomenon and theoretical speculation. There is no doubt that the application of stem cell theory to study the tumorigenesis mechanisms will help change the research and the understanding of the essence of cancer, supplying a new way to effectively diagnose tumor sites and find functional proteins as potential therapy targets. Therefore, CSC theory plays a significant role both in studying the origin of cancer and in clinical practice.

References