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Extra Views

Cancer Stem Cells Persist in Many Cancer Cell Lines

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cancer stem cells, side population (SP), ABC transporter, BCRP1, C6 glioma cell line

ABSTRACT

Both stem cells and cancer cells are thought to be capable of unlimited proliferation. Paradoxically, however, some cancers seem to contain stem-like cells (cancer stem cells). To help resolve this paradox, we investigated whether established malignant cell lines, which have been maintained over years in culture, contain a subpopulation of stem cells. We have shown that four cancer cell lines contain a small side population (SP), which, in many normal tissues, is enriched for stem cells of the tissue. We have also shown that SP cells in C6 glioma cell line, but not non-SP cells, can generate both SP and non-SP cells in culture and are largely responsible for the in vivo malignancy of this cell line. We propose that many cancer cell lines contain a minor subpopulation of stem cells that is enriched in a SP, can be maintained indefinitely in culture, and is crucial for their malignancy.

There is accumulating evidence that cancers, like normal organs, may be maintained by a hierarchical organization that includes stem cells, transient amplifying cells (precursor cells), and differentiated cells.[1-5] Malignant gliomas, for example, contain both proliferating cells and differentiating cells expressing either neuronal markers or glial markers, raising the possibility that they may contain multipotent neural-stem-cell (NSC)-like cells.[6-9] This idea is supported by recent findings that malignant gliomas can be generated from both NSCs and glial lineage cells, such as oligodendrocyte precursor cells or astrocytes, which can behave as NSCs in appropriate conditions.[10-17]

There is other evidence that cancers might contain cancer stem cells. Although many anti-cancer drugs have been used to eliminate cancers, some cancer cells usually survive, and the cancer reoccurs, indicating that the surviving cells are not only resistant to such anti-cancer drugs but are also malignant. It was shown that various ATP binding cassette (ABC) transporters, such as the multi-drug resistant gene (MDR), the multi-drug resistant protein (MRP), and the breast cancer resistant protein (BCRP1), contribute to the drug resistance in cancers.[18,19] Interestingly, some of these transporters are also expressed in many kinds of normal stem cells. BCRP1, for example, excludes the fluorescent dye Hoechst 33342, identifying a side population (SP), which is enriched for stem cells.[20-22] Together, these findings suggest that cancers might contain an SP that is enriched for cells with the characteristics of cancer stem cells.

Cancers can also recruit stem cells from other tissues, including bone marrow (BM)-derived stem cells,[23-25] hematopoietic stem cells[26] and NSCs.[27] BM-derived stem cells, for example, contribute to angiogenesis and support tumorgenesis; when such stem cells are eliminated in vivo, the growth of a transplanted tumor is significantly inhibited.[25] Thus, both endogenous (cancer stem cells) and exogenous stem cells (normal stem cells) seem to contribute to tumorgenesis, making it difficult to identify and isolate bona fide cancer stem cells from freshly-isolated tumors.

Many cancer cell lines have been established that can be maintained indefinitely in culture and form tumors like the original one when transplanted in vivo. Because many such cell lines were derived from single cancer cell, it seems likely that they do not contain any contaminating non-cancer stem cells, making these cell lines attractive models to investigate cancer stem cells.

We recently addressed whether the established cancer cell lines contain an SP. We found that four cancer cell lines, C6 glioma cell line, MCF7 breast cancer cell line, B104 neuroblastoma cell line and HeLa adenocarcinoma cell line, which have been maintained in culture for decades, contain an SP. We have also found that the combination of platelet-derived growth factor and basic fibroblast growth factor is sufficient to maintain SP cells in the C6 glioma cell line. Moreover, FACS-sorted C6 SP cells, but not non-SP C6 cells, could generate both SP and non-SP in culture and form metastatic tumors in nude mice. Thus, the C6 SP contains cells with characteristics of both stem cells and cancer cells.[28]

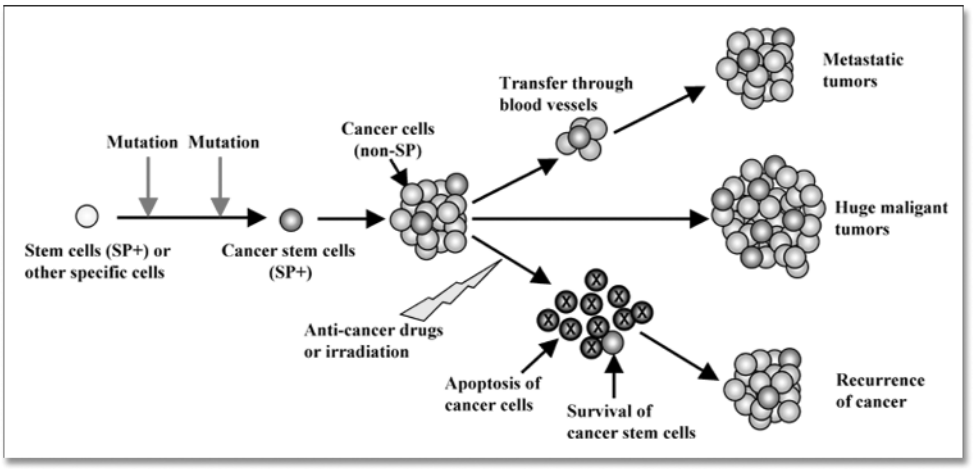

Figure 1. The roles of cancer stem cells in malignncy. Cancer stem cells are thought to be arised from either stem cells or some specific cells, which can revert to stem cells. The cancer stem cells self-renew, generate cancer cells and form huge malignant tumors. Small cell aggregates containing cancer stem cells transfer through blood vessels, invade into other tissues, and form metastatic tumors. Both anti-cancer drugs and irradiation cause cancer cells to die by apoptosis, however cancer stem cells might survive and regenerate cancer.

Very recently, it was shown that acute myeloid leukemias and breast cancers contain cancer stem cells that are responsible for their malignancy.[29,30] Together with our findings, these results suggest that many of cancers might contain their own stem cells, which are responsible for their malignancy (Fig. 1). Because these cells must be eliminated to cure the cancer, there is a pressing need for methods to identify and isolate cancer stem cells so that their properties, including their sensitivity to various anti-cancer therapeutic agents, can be characterized. Our findings provide a simple and general strategy for doing so.

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