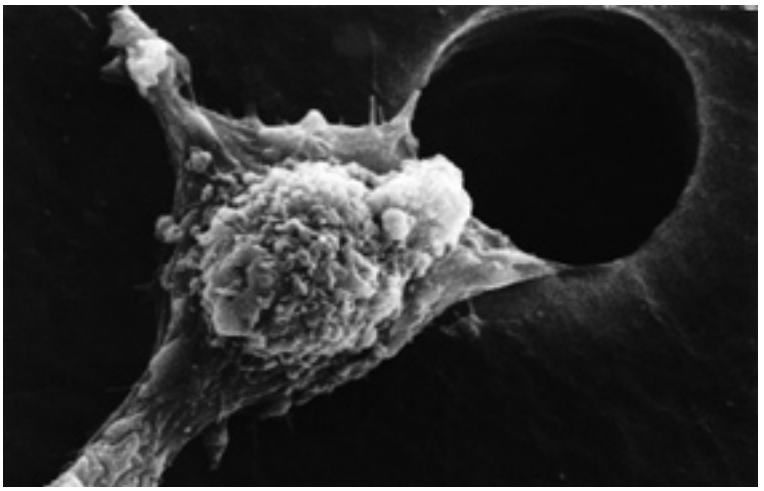


Figure 1. Metastatic cells can migrate to other parts of the body and cause secondary cancers.

credit: Dr. Raouf Girguis/NCI/NIH

Stem cells and cancer

Cracking the ultimate medical code

By Monica Liu

Stem cell research has often been hailed as the new frontier of medical investigation, a scientific field fertile with theoretical insights and clinical possibilities. Embryonic and adult stem cells have the capacity for self-renewal as well as an ability to differentiate into mature, tissue-specific cells. These characteristics are markers for a wealth of possibilities, from a better understanding of the processes that drive human development to the ability to regenerate diseased tissues for cell-based therapy. The debate over the ethical ramifications of embryonic stem cell research has of course been heated and widely publicized, but it oftentimes masks a less prominent but perhaps more important discussion about the role of adult stem cells in human cancer.

Stem Cells and Cancer: The Medical Mystery of the 21st Century

Cancer, which is characterized by abnormal cell proliferation that leads to uncontrolled tumor growth, is a leading cause of death worldwide (7.4 million deaths in 2004)· Scientists have focused on the biological mechanism of tumor formation in an attempt to develop well-informed, effective cancer treatments that slow or halt the progression of the disease by reducing the size of the tumor or eliminating its presence entirely. The conventional model of tumor formation - which holds that tumors arise from mutated somatic cells that have lost the ability to regulate their own growth and division - makes biological sense, but this model does not explain why many cancers recur even after drug therapy successfully minimizes the size of malignant tumors (2).

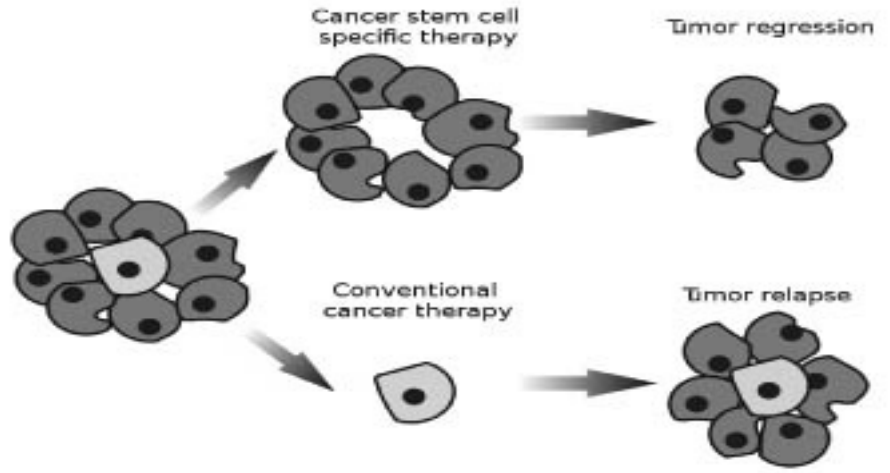
The obvious rift between the theoretical understanding of cancer and the limited success of drug therapies in practice is a medical mystery that years of basic science research and drug development have failed to unravel. Recent studies and observations, however, point to a modified tumor formation model in which a small population of "cancer stem cells" is ultimately responsible for tumor growth and is resistant to currently available therapies. If validated, this new model may transform the way cancer therapies are designed and delivered.

The Origins of the Cancer-Stem-Cell Hypothesis

While the concept that stem cells have many of the same properties (i.e. self-renewal) as cancer cells is firmly

established (3), only recently have scientists been able to employ techniques to identify the presence of these stem cells in tumors. In 1997, University of Toronto-molecular biologist John Dick first identified stem cells in acute myeloid leukemia (AML) (4). Dick et al.. found that when AML cells were labeled with two antibodies linked to fluorescent tags, the large majority of cells were positive for both antibodies, while a minority population consisting of what Dick et al.. predicted to be cancer stem cells only expressed the CD34 antibody. Dick et al.. confirmed that the CD34-positive cells, which accounted for as little as 0.2% of the total cell count, were cancer stem cells by documenting tumor formation and growth in mice injected with these cells. Since it is more difficult to separate cell populations in solid tumors than in blood, most of the data available are associated with leukemia. However, evidence for the presence of small fractions of cancer stem cells in tumors of the brain, pancreas, lung, ovary, bladder, etc. is abundant (5).

Further investigation revealed that this reservoir of cancer stem cells may be more resistant to cancer therapy than normal tumor cells and may also be responsible for the generation and propagation of mutant cells that are relatively immune to treatment. Jeremy Rich et al.. used a mouse model to show that cancer stem cells are more likely to survive radiation therapy than other tumor cells (6). All of the cells were killed when Rich et al. combined the radiation therapy with a DNA repair inhibitor, suggesting that cancer stem cells may have an inherent advantage for cell survival. Chang et al. at the Baylor College of Medicine in Texas obtained similar results when they tested the stem-cell hypothesis in breast cancer: while an increased post-chemotherapy proportion of cancer stem cells indicated that treatment was effective only on non-cancer stem cells, the addition of a drug that blocks the HER2 cell differentiation pathway restored the original cancer stem cell: normal tumor cell proportion (7).



▲ Figure 2. Cancer stem cells may be able to survive conventional cancer therapies, which can potential result in relapse of the cancer and regrowth of the tumor. New cancer cell specific therapies must be designed to prevent such relapses.

All of these conclusions support the recently minted cancer-stem-cell hypothesis, which proposes that a rare population of stem cells that can no longer regulate their own population size initiate and maintain malignant tumors and contribute to their resistance to cancer treatment (8).

The Challenges Ahead

When stem cells divide, each cell generates a progenitor cell and a new cell capable of self-renewal. According to the cancer-stem-cell hypothesis, mutations that accumulate in these self-renewing cancer stem cells drive tumor growth and eventual metastasis. Since a plethora of studies of various malignant cancers support the cancer-stem-cell hypothesis of tumor formation and maintenance, cancer stem cells have emerged as attractive targets for therapeutic agents that select specifically for these cells. Thus, the cancer biology community has recently begun to focus on finding drug targets for cancer stem cells, an approach that may result in more durable responses to treatment as well as possible eradication of metastatic tumors.

A popular tool for identifying appropriate drug targets is gene expression profiling, which involves the analysis of tumors on microarrays that reveal differences between cancer stem cells and normal tumor cells that cannot be identified pathologically (9). For example, While microarray analysis facilitates the separation of tumor cell types into groups that reflect different mutations, the high normal tumor cell: cancer stem cell ratio present in many tumors often generates a composite expression profile that is more representative of the function of normal tumor cells than of the cancer stem cells of interest (10). Microdissection of morphologically similar clusters of cancer cells or histological staining of tissue sections have also been used to create gene expression profiles that inform drug development efforts. For example, Guo et al. combined profiling with histological analysis of paraffin-embedded tissue samples to associate a deletion in the Pten gene with a myeloproliferative disorder (11). Purifying cancer stem cells from the tumor before performing gene-expression profiling on the isolated cells would allow investigators to eliminate irrelevant gene expression data, but this approach still requires much technical refinement. Scientists are currently testing drugs

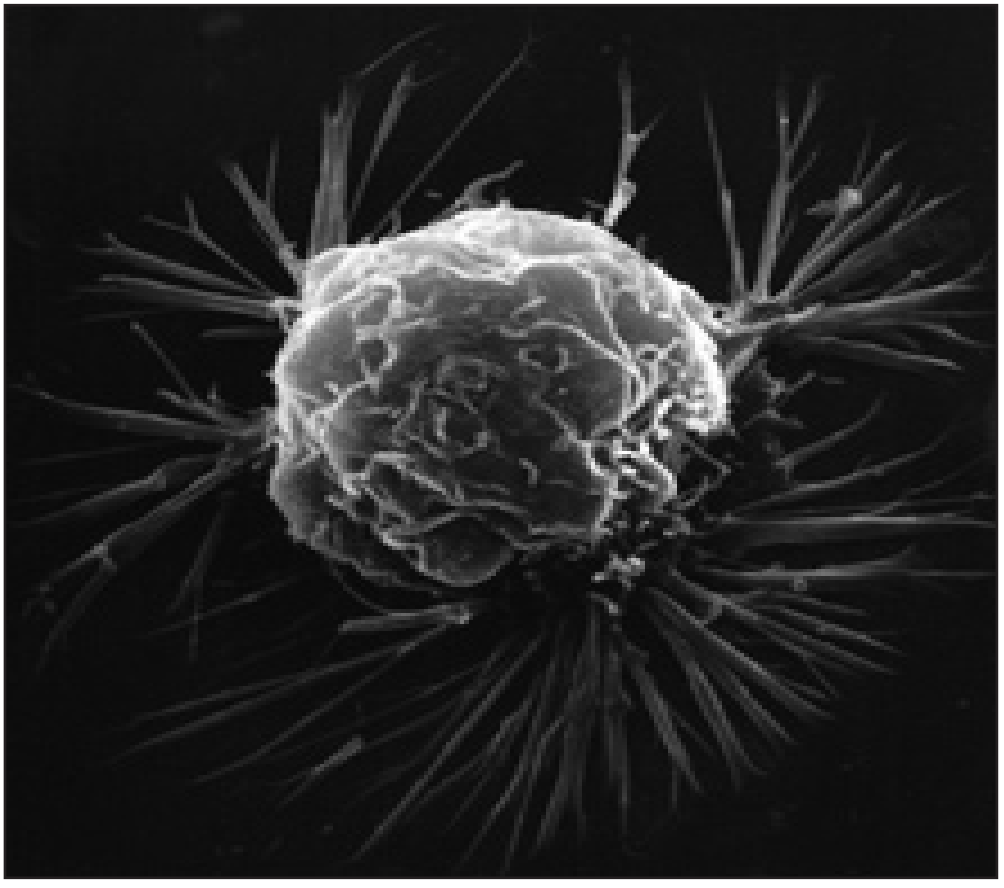


Figure 3. A breast cancer stem cell.

credit: http://www.epa.gov/region5fields/htm/methods/gps/index.html

that hit targets identified by numerous cancer-stem-cell studies. For example, MK0752, a drug developed by Merck that inhibits Notch, the self-renewal gene in stem cells, is currently being paired with conventional chemotherapy treatment in a new drug trial. While there is concern that MK0752 will kill both normal stem cells and cancer stem cells, both of which utilize Notch, preliminary results in mouse models indicate that normal stem cells survive when treated with the Notch inhibitor drug (12).

Though the numerous basic science findings and clinical investigations on cancer stem cells are promising, these studies face serious challenges. For example, the stem-cell-hypothesis has been criticized by those who argue that it relies too heavily on inferences from animal models, which do not necessarily represent the molecular operation of cancer in humans. However, recent advances in xenotransplantation techniques are making great strides in reducing the difference between animal models and human responses to disease (13). In addition, the unique population of cancer stem cells is extremely difficult to pinpoint in tumors, as the phenotypes, functions, and signaling pathways of cancer stem cells are extremely similar to those of normal stem cells. While Jin, et al.. recently showed that monoclonal antibody-mediated targeting of the CD44 cell surface marker eradicated cancer stem cells in immunocompromised mice without causing toxicity to normal cells, imprecise targeting continues to render most therapeutic agents only partially effective against malignant tumors (14, 15).

"Cancer stem cells may be...responsible for the generation and propagation of mutant cells that are relatively immune to treatment"

Conclusion

Stem cell research commands the scientific spotlight of the 21st century. Much of the basic science behind the stem-cell-hypothesis has yet to be discovered, from the precise molecular disparities between normal and cancer stem cells to the the question of whether cancer stem cells are the causes or byproducts of cancer. In the clinical arena, linking cancer stem cell-targeted treatments with permanent tumor reduction shows great potential but limited practical success.

Regardless of the challenges, the current body of research suggests that further studies may unravel the mystery of cancerous stem cells and may lead to the development of enhanced, less invasive treatments for certain cancers. Tying informative basic science research to novel clinical developments may one day allow patients to view cancer as less of a death sentence and more of a treatable, curable ailment. H

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