Cancer Stem Cells

A Gateway Towards Novel Cancer Therapeutics

By Francisco Galdos

In 2012 alone, the American Cancer Association estimates that 577,190 Americans are expected to die of cancer this year (1). Cancer is defined as a group of diseases characterized by the uncontrolled and abnormal growth of cells (1). As cancer is the second most common cause of death in the US, cancer research has long been focused on understanding the biological mechanisms by which the disease originates and spreads throughout the human body.

For many years, it was believed that cures for cancer were within reach. Since 1971, the US government has actively been involved in the infusion of resources to conquer the 'war against cancer' (7). Despite extensive research efforts and advancing treatments, the resurgence of cancer in patients has continued to contribute to mortality and has posed difficult questions regarding cancer growth and development (11). Interestingly, the fight against cancer has been complemented by concurrent growth in the field of developmental and stem cell biology. The merging of stem cell biology and oncology has inspired new ideas and approaches towards the study of cancer, particularly in terms of deciphering appropriate biological models for tumor growth (11).

Traditionally, cancer researchers have accepted the stochastic (clonal) model for cancer development, which assumes that most cancerous cells have tumor forming potential (11). Recently, in three separate studies, researchers have provided the first direct evidence supporting the Cancer Stem Cell (CSC) model for cancer growth. The CSC model proposes a novel way to combat cancer that involves moving away from the traditional model for shrinking tumor size, and instead specifically targets the source of cancer, namely the CSCs. These studies have energized discussions on what many researchers believe is a revolution in the way cancer is currently understood and treated (2,3,4).

The CSC Model Explained

The stem cell concept as it relates to cancer dates back to the nineteenth century when similarities were noted between tumors and embryonic tissue (7). During early mammalian development, the cells composing the embryo are known as embryonic stem cells (7). These cells have the ability to form all other cells of the body, and as development continues they begin to differentiate into many types of tissues and cells. Many of these tissues contain partially specialized subsets of stem cells that help regenerate cell types within specific tissues and can often become malignant and develop into tumors (7). In the 1980s, it was discovered that transplanting a single malignant stem cell from one mouse to another, could give rise to entire tumors called teratomas in the transplanted mouse. This gave rise to the CSC concept that defined the subset of stem-cell-like cells as the drivers of tumor growth (7).

Until recently, much of the evidence for CSCs has come from transplantation experiments which involve transplanting tumor tissue into immunodeficient mice

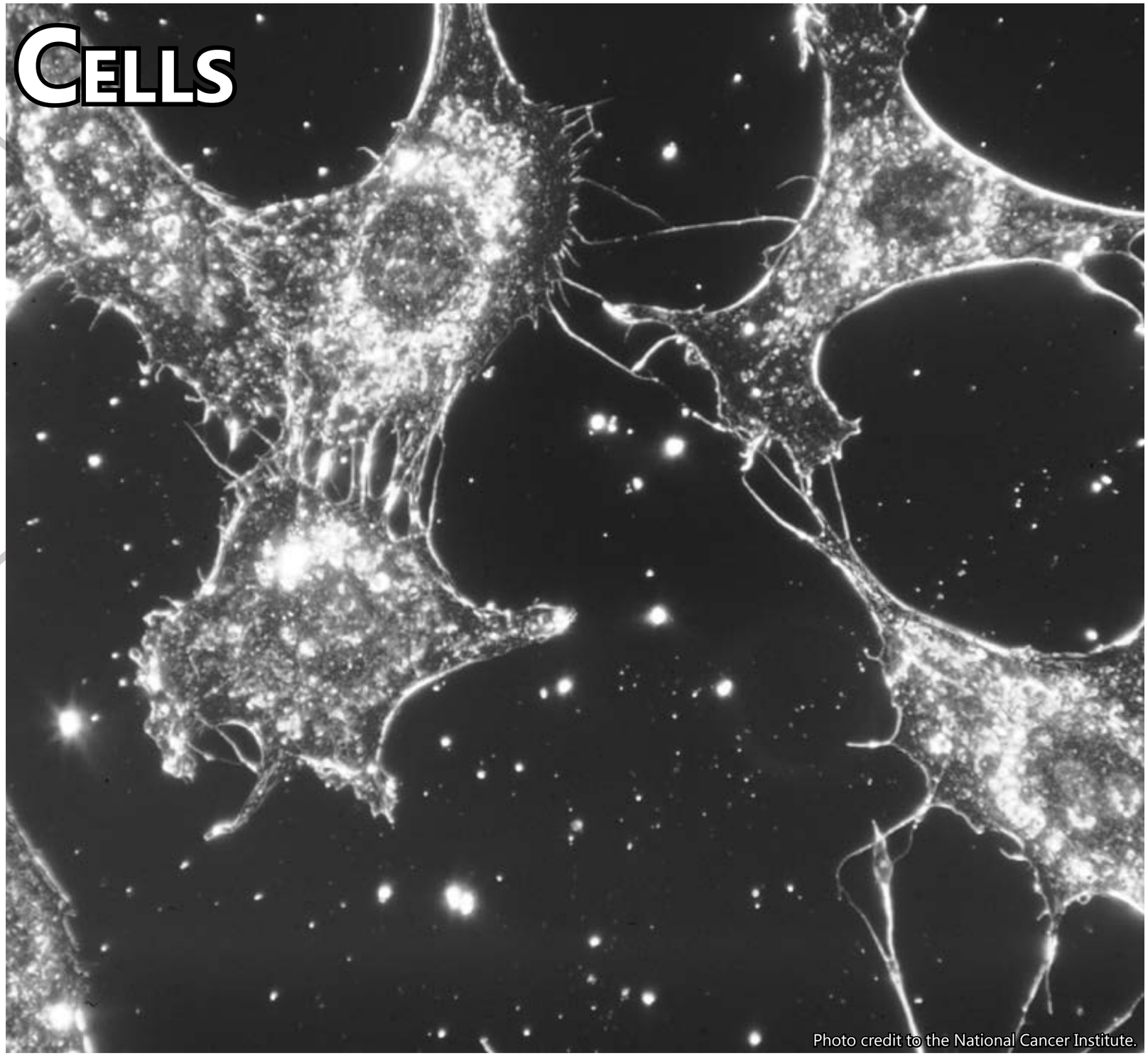

Photo credit to the National Cancer Institute.

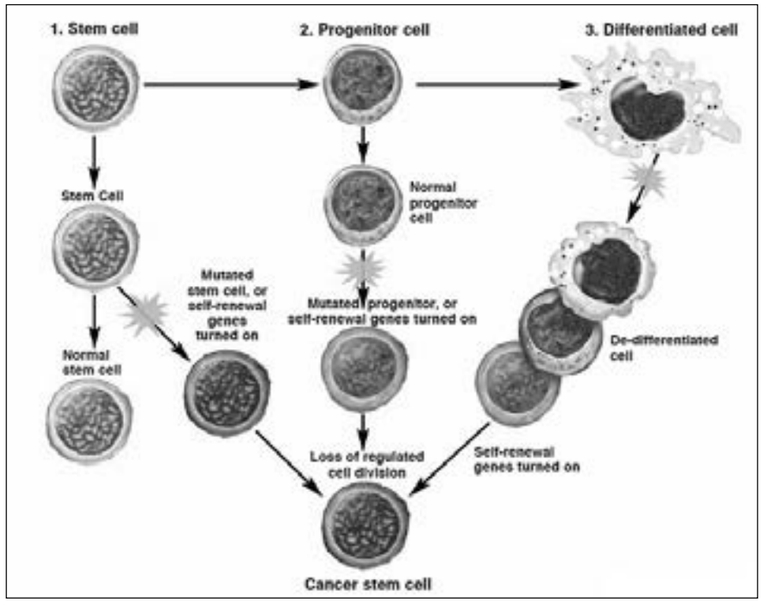

Figure 1: Flow chart showing the different types of cell from which a cancer stem cell can arise. ***Photo credit to National Institutes of Health.***

as a way to prove that CSCs can form a tumor in another individual (7). These experiments have been done to study acute myeloid leukemias, breast cancer, and certain types of brain cancers, all of which have provided preliminary evidence of tumor initiating cells, or CSCs (6). Although these results have been promising, critics of the CSC model have claimed that it dramatically underestimates the number of human cancer cells that have tumor forming potential and does not provide definitive experimental evidence for the existence of CSCs (8, 11). Despite this controversy, the previously mentioned studies, published in August of this year, have provided direct evidence for the existence of CSCs in brain, gut, and skin cancers.

The Big Three

Until now, direct evidence for the existence of CSCs has been elusive. The three aforementioned studies from Luis Para's team of UT Southwestern, Hans Clever's team of the Hubrecht Institute, and Cedric Blanpain team of the Free University of Brussels, have each provided direct evidence for the existence of CSCs in three separate types of cancers.

Luis Parada's team focused on studying a type of brain tumor called glioblastoma multiforme that is often associated with high levels of tumor reoccurrence and cancer relapse after treatment (2). Using a fluorescent genetic technique, Parada's team found that a gene that is indicative of adult neural stem cells was also expressed in a subset of glioma tumor cells. Parada's group was able to show that this subset of glioma cells was driving tumor growth by first administering a chemotherapeutic drug to mice in order to halt tumor growth and then examining the cell targets of the drug. After therapy was stopped, Parada's team found that tumor growth reinitiated and that a high percentage of the new tumor cells originated from the fluorescently marked subset of glioma cells (2). Furthermore, killing the fluorescent stem-cell-like glioma cells significantly reduced long-term tumor growth, providing direct evidence that a subset of glioma cells exhibit properties of cancer stem cells.

Similar to Parada's team, Blanpain's team conducted experiments in skin tumors using a similar technique called lineage tracing. In their experiments, they used a genetic labeling strategy that allows individual tumor cells to be marked and traced over time at different stages of tumor progression (3). They found that the majority of labeled tumor cells in benign skin papilloma limited proliferative potential, and only a fraction has the capacity to persist, giving rise to progeny cells that make up a significant part of the tumor (3). Through quantitative measurement of clone colonies in invasive squamous cell carcinoma, the Blanpain group found that the expansion of the colonies was consistent with that of a single CSC population, effectively presenting the first experimental evidence for the existence of CSCs during unperturbed solid tumor growth (3).

The Clever study provided evidence for the presence of stem cell activity within primary intestinal adenomas, a precursor to intestinal cancer (10). Similar to the Parada study, Clever found that subpopulations of adenoma cells fuel the growth of established intestinal adenomas. These subpopulations express the same genetic marker as intestinal stem cells (10). All three studies effectively provided evidence for the existence of CSCs, an incredible milestone in cancer research. The issue of how to reconcile both the clonal and the CSC model still remains.

Reconciling Two Models

The most fascinating aspect of these three studies is that they advance a model of cancer that has long been controversial throughout in the scientific community. The traditional model has held that all tumor cells have the potential to give rise to cancerous progeny (11). However, with new evidence showing the existence of CSCs, the two models contradict each other in terms of how they view cancer treatment. The CSC model argues for the direct targeting of cancer stem, while the traditional clonal view argues for targeting all cells in tumors (11). Some researchers believe that therapies based on the clonal view of cancer often fail to eradicate the small proportion of cells that lead to cancer relapse (4).

Perhaps both models are correct. Before the rise of the CSC model, the traditional model provided great advancements in cancer treatments and continues to be an accurate and well-supported model for many cancer types. The problem has been, however, that some cancers, such as those studied by Parada, Blanpain, and Clever studies, are better explained using the CSC model (11). Thus, the CSC model does not replace the long held clonal model, but rather provides a tool for cancer researchers. This powerful tool may well provide insight into treatments that can cure specific types of cancers that have long been resistant towards traditional treatments.

Gateway to Treatment

The CSC model is a powerful tool towards understanding why certain cancers have not reacted well to current treatment options. Perhaps the most incredible aspect of the CSC model is that it identifies a small subset of cells as drivers of cancer. This argument has reenergized the discussion on cancer treatment as it gives rise to an entirely novel field of therapeutics that combines interdisciplinary research between oncology and stem cell biology. It will truly be exciting to see how the CSC model will contribute towards novel approaches in combating cancer. We may well see the advent of treatments that can effectively kill CSCs and stop the growth of cancer at its root.

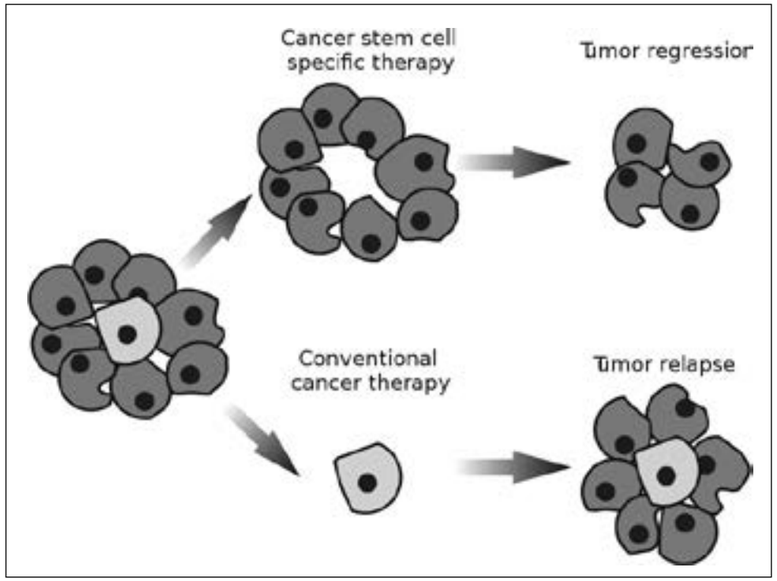

Figure 2: Diagram comparing the results of cancer stem cell specific therapy with conventional cancer therapies in fighting tumors following the CSC model. ***Photo credit to Wikipedia.***

References

1. **American Cancer Society. Cancer Facts & Figures 2012. Atlanta: American Cancer Society; 2012.**
2. **Chen, Jian, Tzong-Shiue Yu, Renee M. McKay, Dennis K. Burns, Steven G. Kernie, and Luis F. Parada. "A restricted cell population propagates glioblastoma growth after chemotherapy." Nature, August 2012: 488, 522-526.**
3. **Driessens, Gregory, Benjamin Beck, Amelie Caauwe, Benjamin D. Simons, and Cedric Blanpain. "Defining the mode of tumour growth by clonal analysis." Nature, August 2012: 527-531.**
4. **Ghosh, Pallab. Cancer stem cell discovery could signal 'paradigm shift'. August 1, 2012. http://www.bbc.co.uk/news/health-19083685 (accessed September 14, 2012).**
5. **Gupta, Piyush, Christine L. Chaffer, and Robert A. Weinberg. "Cancer stem cells: mirage or reality?" Nature Medicine, 2009: 1010-1012.**
6. **Lapidot, Tsvee, et al. "A cell initiating human acute myeloid leukaemia after transplantation in SCID mice." Nature, 1994: 645-648.**
7. **Nguyen , Long V., Robert Vanner, Peter Dirks, and Connie J. Eaves. "Cancer stem cells: an evolving concept." Nature, February 2012: 133-143.**
8. **Nowell, Peter C. "The Clonal Evolution of Tumor Cell Populations." Science, 1976: 23-28.**
9. **Pierce, G. B, and W. C. Speers. "Tumors as caricatures of the process of tissue renewal: prospects for therapy by directing differentiation." Cancer Research, 1988: 1996-2004.**
10. **Schepers, Arnout, et al. "Lineage Tracing Reveals Lgr5+ Stem Cell Activity in Mouse Intestinal Adenomas." Science 337 (August 2012): 730-735.**
11. **Shackleton, Mark, Elsa Quintana, Eric Fearon, and Sean Morrison. "Heterogeneity in Cancer: Cancer Stem Cells versus Clonol Evolution." Cell, no. 138 (September 2009): 822-829.**

Many thanks to my editor Yvette Leung for helping me with revisions, and for my good friends Yacine Fares, and Eugene Wang for providing me with feedback during the revision process.

— Francisco Galdos '15 is a Human Developmental and Regenerative Biology concentrator in Currier House.