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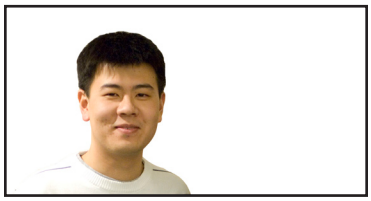
Paradigm Shift: Cancer Stem Cells



Kevin Wang

Despite rapid technological advancements, cancer remains to be one of the leading causes of mortality. Since the introduction of chemotherapy and radiation nearly half a century ago, there has been little advancement in cancer treatment. The present article will examine the cancer stem cell hypothesis, which is proving to be a promising model that may lead to novel therapy targets.

"We have to find something that walks like cancer, talks like cancer, but isn't cancer."
"Cancer stem cells are real!"

Such were the words of Dr. Gregory House (from popular TV series, *House*) as he elucidated the presence of cancer stem cells. It has long been known that cancers originally develop from one or a few normal cells that acquire the ability to proliferate and metastasize. Yet, the origin of these tumours remains a mystery. Only recently has the discovery of cancer stem cells begin to shed light on the underlying mechanisms of oncogenesis. This potential paradigm shift in cancer biology may one day lead to the development of new treatment strategies that target the heart of a tumour by attacking the cells that initiate them.

Properties of Stem Cells

In order to understand the Cancer Stem Cell (CSC) hypothesis, we must first revisit the basics of stem cell biology. In the early stages of human life, a totipotent pool of cells differentiate into the germ layers, each of which further develop into tissue types in the body. The genesis of new cells occurs through a small pool of somatic stem cells that are responsible for the development and maintenance of tissues throughout one's lifetime. These somatic stem cells have the capacity to self-renew and differentiate into one or more mature cell types (Figure 1). Each division gives rise to two daughter cells, a stem cell and a progenitor cell. The stem cell renews the stem cell pool and the progenitor cell loses the power to self-renew but acquires the ability to differentiate into mature cell types (Lobo et al., 2007).

In normal tissues, these self-renewing stem cells can differentiate into progenitor and mature cells depending on their microenvironment (Bjerkvig et al., 2005). Unregulated proliferation is prevented by restricting the stem cells' ability to self-renew. Cancer stem cells have similar self-renewal and differentiation ability as stem cells, except its growth is unregulated.

Evidence of Cancer Stem Cells

The stochastic theory of oncogenesis fails in its inability to explain two important observations in cancer growth (Lobo et al., 2007). For decades, scientists have observed that most tumours arise from a single cell, but not all the cells within the

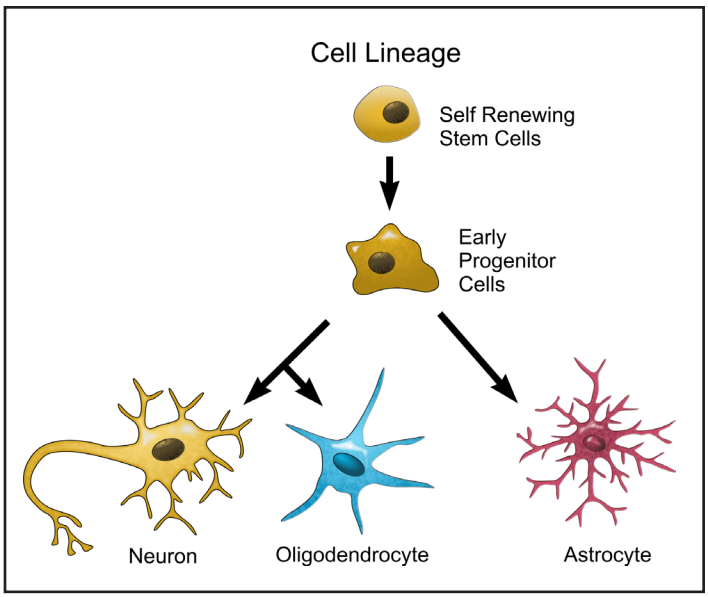


Figure 1 Normal stem cell differentiation to different lineages of nerve cells (NINDS, 2005).

tumour are identical, a concept known as tumour heterogeneity (Heppner, 1984). This diverse morphology cannot be explained by a somatic cell that has acquired the ability to proliferate as it cannot differentiate into different cell types. The CSC hypothesis, on the other hand, is able to explain this anomaly through the generation of a pool of progenitors, each of which, depending on its cellular niche, can differentiate into the desired cell type (Calvi et al., 2003). In many cancers, portions of the tumour are cancerous, while others are "normal" cells that support the growth of the tumour.

The second observation stems from the observation that, despite the stochastic model suggesting that a single cell can generate a tumour, at times even large numbers of cancerous cells fail to do so (Lobo et al., 2007). If all the cells within a tumour have the same proliferative potential, one would assume that even a few cells can recapitulate the original tumour, yet this has not been demonstrated in the lab. The CSC hypothesis postulates the existence of a cellular hierarchy whereby only a small population of the tumour is capable of self-renewal and thus generating a new tumour. As the cancer stem cells proliferate, a large pool of progenitors is responsible for the bulk of the tumour, yet these cells only have a limited capacity to replicate and cannot initiate tumour formation *de novo.*

Another observation stems from mutations that give rise to cancers. Despite rigorous regulatory mechanisms, mutations that result in aberrant proliferation during mitoses do occur. Many of the tissues in which malignancies originate are composed of short-lived cells such as skin, or blood. Many cancers require a specific series of mutations involving signal transduction, cellular control, and DNA repair mechanisms. These differentiated progenies are often protected from genotoxic stresses due to their relatively shorter life-span. Stem cells may be preferential targets of initial oncogenic mutations, as they are maintained throughout a person's lifetime, thus have many opportunities to accumulate mutations (Lobo et al., 2007).

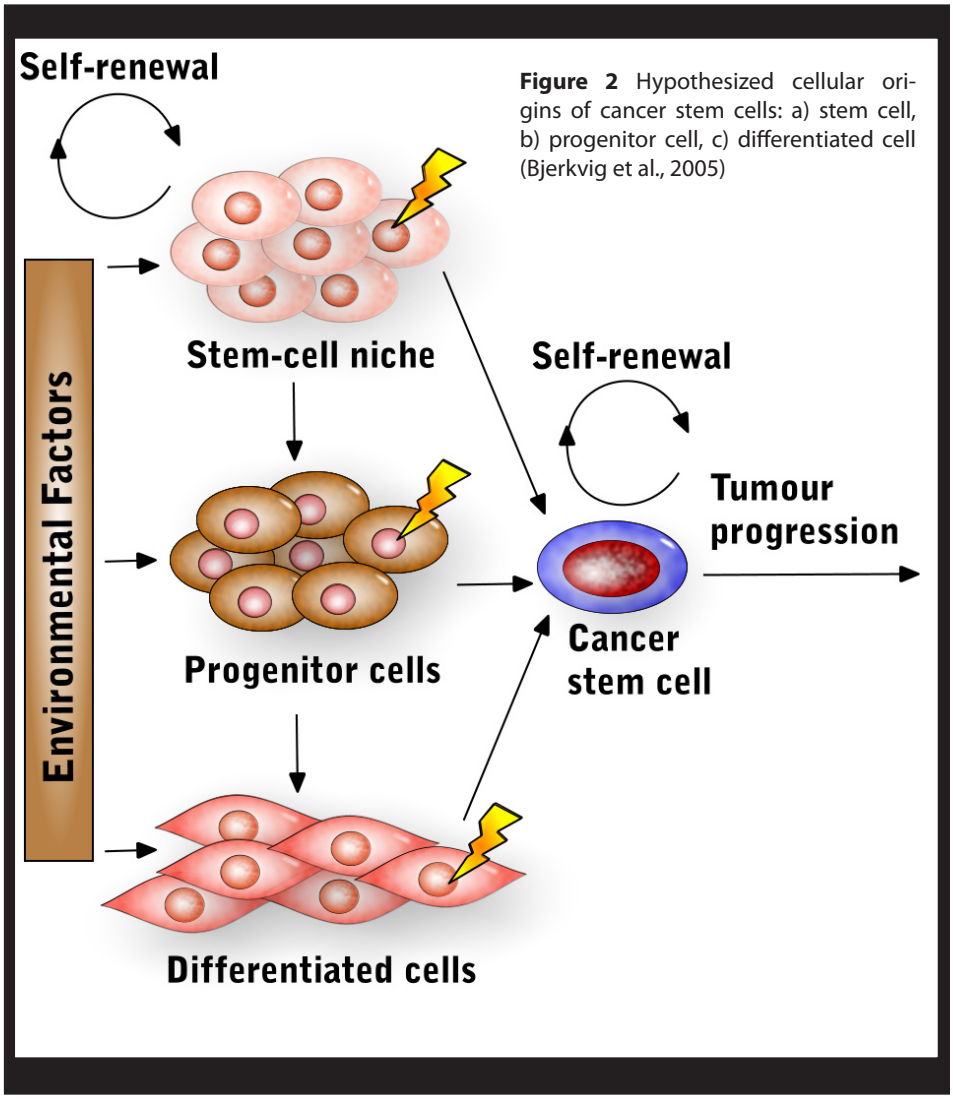


Figure 2 Hypothesized cellular origins of cancer stem cells: a) stem cell, b) progenitor cell, c) differentiated cell (Bjerkvig et al., 2005)

Cancer Stem Cells in Different Tissues

Leukemia

The existence of stem cells began with the discovery of hematopoietic stem cells by Till and McCulloch in 1961. They were able to demonstrate clones that could give rise to multilineage colonies consisting of different blood cells (Till & McCulloch, 1961). Fittingly, the first discovery of cancer stem cells also took place in hematology. John Dick's group at the University of Toronto was the first to isolate a population of primitive hematopoeitic stem cells in acute myeloid leukemia (AML) in 1997 (Bonnet & Dick, 1997). This small population of tumour cells, characterized by surface markers CD34+CD38-, when transplanted into recipient mice, was able to recapitulate the phenotypic profile of the original cancer.

Breast Cancer

In order to substantiate the CSC theory, it became critical to isolate stem cell populations in other cancer types. To find CSCs in solid tumours became the Holy Grail in the field as the surface markers required to isolate CSCs were still unknown. In 2003, Michael Clarke's lab succeeded in finding CSCs in breast tumours. In a mouse model, as few as 100 breast cancer stem cells (CD44+CD24-) injected into the breast of healthy mice formed tumours, whereas tens of thousands of other cancer cells isolated from the same original tumour were unable to do so (Al-Hajj et al., 2003; Dontu et al., 2003).

Brain Cancer

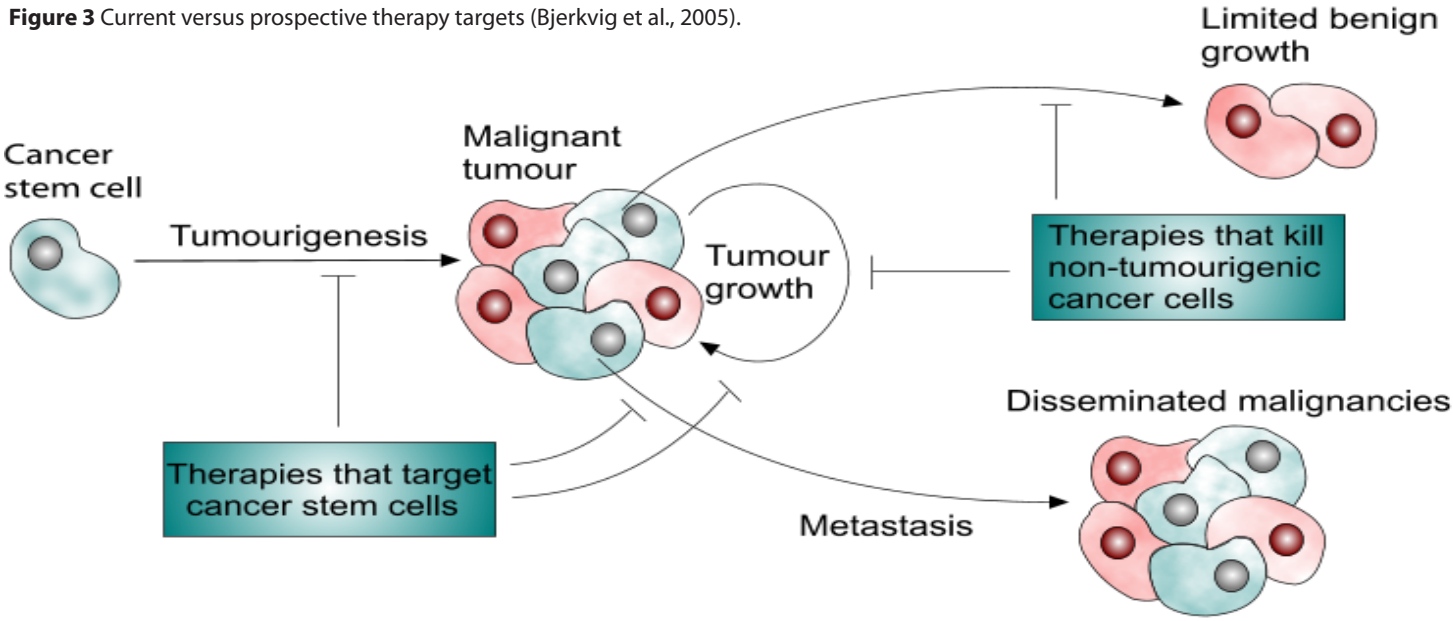
CSC in the central nervous system was another hard-sought trophy due to the long-held dogma that brain tissue becomes quiescent in adulthood. In 2004, Sheila Singh, formerly at the University of Toronto (now a scientist at the McMaster Stem Cell and Cancer Research Institute), identified similar stem-like cells in human brain tumors. These CSCs, composing a much smaller portion of the tumour were isolated using the marker CD133. In a mice xenotransplantation model, it was demonstrated CD133+ tumour cells were able to generate the original tumor even when 1000 fold increase in the CD133- population were unable to do so (Singh et al., 2004). Since this discovery, CSCs were identified in several other tissue malignancies including melanoma, bone, ovarian, prostate, and colon cancers (Fang et al., 2005; Gibbs et al., 2005; Bapat et al., 2005; Collins et al., 2005; O'Brien et al., 2007).

Cancer Stem Cell Biology

Since the discovery of CSCs, one central question involves the cellular origin of these cells. As both CSCs and normal stem cells must renew themselves and induce differentiation, it is reasonable to assume some molecular mechanisms are shared. Even though researchers have been able to isolate CSCs from tumours, no one has been able to differentiate CSCs from their normal counterparts as they often share the same molecular markers (Lobo et al., 2007). It remains to be elucidated whether it is the progenitors which have accumulated mutations and now can revert back to a CSC, or whether it is the normal stem cell transforming into a CSC (Figure 2). Recent evidence is showing that both are possible; however, the molecular pathways that lead to these transformations remain to be discovered (Bjerkvig et al., 2005).

Regulation of stem cell functions has become a rapidly growing research field. Studies published in 2003 by Molofsky and Sauvageaou independently demonstrated the role of polycomb-group protein, Bmi-1, as crucial in the self-renewal of CSCs (Molofsky et al., 2003; Lessard & Sauvageau, 2003). In patients with AML, expression of Bmi-1 is much higher than in normal bone marrow, indicating a potential relationship in causing oncogenesis. Another important pathway that is associated with many types of cancer is the Wnt/β-catenin pathway. Although crucial in normal development, they have been implicated in the self-renewal of CSCs (Reguart et al., 2005).

Figure 3 Current versus prospective therapy targets (Bjerkvig et al., 2005).



Clinical and Ethical Considerations

Despite the vast amount of resources invested into cancer research, the prospect of a cure has long eluded scientists. The CSC hypothesis may one day provide the answer to a cure. From a clinical point of view, it becomes necessary to target CSCs while not harming the normal stem cells that are vital to tissue growth and repair. Many current chemotherapies target the bulk of the tumour mass, which may explain the high likelihood of relapse. Current therapies operate under the assumption that all cancer cells have equal malignant potential. Thus, in many cases, a small population of cells remains after treatment. In fact, recent reports have shown that CSCs are more resistant to conventional therapies, including chemotherapy (Costello et al., 2000) and radiation (Bao et al., 2006). Future treatment strategies must focus on targeting and eliminating the CSCs which drive the growth of the tumour (Figure 3).

The study of cancer stem cells have come under much scrutiny due to the use of embryonic stem cells (cells obtained from aborted fetuses). In Canada, there is a relative freedom in scientists' access to rare stem cell samples, but this is not the case for many other nations including the United States (however this is rapidly evolving under the new Obama administration). Despite the promising new findings, many barriers remain to be overcome before these advances can be translated to patient care.

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