# Cancer Stem Cells: New Paradigm in Cancer

By Luís Carlos de Oliveira

Cancer has presented enormous personal, clinical, and social challenges for centuries. One of the oldest known descriptions of cancer, although it was not recognized as such, was in ancient Egypt where cancer was ultimately blamed on the gods [1]. After decades of research and numerous theories about the biology and treatment of cancer, an important step was reached with the conclusion that cancer was an exception to the famous Koch's postulates. Among other things, the postulates state that a single specific cause must be found for each disease, something that is not true for cancer. This made oncology the first discipline in which the disease process was recognized to be produced by a wide variety of divergent stimuli [2].

Cancer is now well-known to be a genetic disease. It is usually initiated by factors (frequently from the environment) that cause mutations in the cells of the body, although, a subset (5-10%) of cases can be traced back to inherited mutations [3]. This incredible evolution in our understanding of cancer has resulted in an impressive improvement in cancer diagnoses and therapies [4]. However, in spite of all these efforts, conventional therapies and strategies are typically only effective in the first phase of cancer treatment. Many patients show intrinsic or acquired treatment resistance that leads to relapse. A recent theory to explain this phenomenon is born out of growing evidence that many types of cancer originate from - and are constantly fed by - a group of cells termed cancer stem cells (CSCs). These cells display relative resistance to radiation and chemotherapy while also promoting activities such as blood vessel growth within the tumor, leading to sustained tumor growth [5].

As also discussed in a companion article in this issue, several recent studies have identified so-called CSCs in colorectal, breast, ovarian, pancreatic, prostate, head and neck, melanoma, hematopoietic, hepatic, lung and brain tumors [6, 7]. These cells are defined by several qualities, including an extensive capacity to self-renew, an ability to initiate cancer after being implanted into a new location, chromosomal or gene alterations, the capacity to generate non-tumorigenic cells, and the ability to become different types of cells [8]. Despite this understanding of what CSCs are and do, there are still many open questions, including how to distinguish CSCs from normal stem cells (NSCs), and what role CSCs play in resistance to chemotherapy. Two recent studies now provide much-needed insights into these critical questions.

The first study, from Nakanishi et al., reports an important challenge: the identification of a specific marker for intestinal CSCs. The authors use lineage-tracing experiments (experiments that show where specific cell types end up) to show that the protein doublecortin-like kinase 1 (Dclk1) does not mark NSCs in the intestine but instead is a unique marker for CSCs that continuously produce tumor progeny in the polyps of $Apc^{Min/+}$ mice. Additionally, the authors propose that leucine-rich repeat-containing G-protein coupled receptor 5 (Lgr5), a cell surface membrane protein, is a partner of Dclk1. However, it is possible that other proteins found on the surface of stem cells may substitute for Lgr5. Removing Dclk1-expressing CSCs resulted in a regression of polyps with no apparent damage to the normal intestine, leading the authors to propose Dclk1 as a target for the treatment of colorectal cancer [9]. The role of Lgr5 in primary intestinal adenomas was also reported in "lineage retracing" experiments carried out by Schepers et al., who found that -expressing cells could produce copies of themselves as well as other tumor cell types [10].

The involvement of CSCs in therapeutic resistance was confirmed by experiments done by Parada et al., using a genetically engineered mouse model of glioma. In a study published in *Nature*, the authors identified a subset of endogenous tumor cells that produce new tumor cells following temozolomide-based chemotherapy. They proposed that this otherwise relatively quiescent subset of cells (with similar properties to cancer stem cells) are responsible for sustaining long-term tumor growth by producing transient populations of highly proliferative cells [11]. In support of this, as recently reviewed by Baumann et al., multiple studies have shown loco-regional or meta-

static spread in patients following radiotherapy or combination treatments, potentially due to a failure to eradicate CSCs [4].

By identifying and understanding the pathways involved in CSC self-renewal, researchers may be able to generate targeted therapeutics that inhibit them [7]. Several innovative therapeutic agents are being studied. One potential class of agents is anti-sense miRNA oligonucleotides (AMOs). These agents function by targeting a microRNA (miRNA) produced in CSCs, binding to and blocking the miRNA. Alternatively, other approaches targeting miRNAs are using miRNA to directly increase expression of tumor suppressive miRNAs expressed in CSCs, producing an anti-cancer effect. Recent studies have explored these agents to eliminate CSCs by interfering with several oncogenic pathways [12]. Lin et al. reported for the first time that one miRNA, miR-143, had increased expression during the differentiation of prostate cancer stem cells and also promoted metastasis. This was due to miR-143 repressing expression of a protein that regulates cell motility, Fibronectin type III domain containing 3B (FNDC3B). Using antisense oligonucleotides to silence miR-143 resulted in suppressed prostate cancer cell migration and invasion *in vitro,* and systemically inhibited metastasis *in vivo* [13].

In conclusion, the introduction of the CSC concept has led to some important advances in cancer research, but there are still many issues to be understood. To this end, the Cancer Stem Cell Consortium (CSCC) recently prioritized the identification of biomarkers and anti-CSC therapeutic agents [14]. The recent studies highlighted here will help researchers build a more detailed picture on how CSCs contribute to cancer, pushing forward our understanding of cancer biology and hopefully driving new therapies while creating new hopes for cancer patients.

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