Cancer Stem Cells: The "stem" of a wicked plant?

By Laura Ghisolfi, Ph.D.

Most multi-cellular organisms have numerous different types of stem cells, which, through the cell division and differentiation process, mature into highly specialized cells that comprise tissues. One example of this is the bone marrow stem cells that generate red blood cells, white blood cells and platelets. Stem cells are also able to self-renew, meaning they can generate copies of themselves and provide a renewable pool of cells to support continued tissue regeneration.

In a similar manner, a new theory of cancer biology is that tumors also contain a population of cells that self-renew and give rise to the more differentiated and specialized cancer cells that form the tumor. Known as cancer stem cells (CSCs) [1], these cells are not only believed to be responsible for tumor growth and maintenance, but they may also drive tumor recurrence, metastasis, and resistance to radiation and/or chemotherapies [2]. At a molecular level, CSCs and normal stem cells share some common features, including activation some of the same cellular pathways that regulate their "stem status" (stemness) and their ability to self-renew. However, CSCs do not appear to differentiate into cells of multiple tissues like normal stem cells do. Therefore, normal stem cells and CSCs are, in a sense, siblings, but not identical twins.

Where CSCs come from remains an open and intensely researched question. Some researchers propose that CSCs may originate from mutated normal stem cells upon aberrant alteration of the self-renewal pathways [3]. An alternative hypothesis is that CSCs originate from non-stem cells that have acquired stem-like features following multiple mutations to their DNA. These features include the ability to indefinitely self-renew and generate different types of tumor cells, among others [4].

According to the cancer stem cell theory, cells derived from a pioneer CSC proliferate and mature to different stages, creating a tumor comprised of a very diverse cell population that is organized in a manner somewhat similar to normal healthy tissues. This model contrasts strongly with the traditional theories regarding tumor growth. According to the traditional stochastic clonal model, one or more cells gain the ability to form tumors after accumulating mutations; these cells then create clones of themselves with infinite lifespan and the ability to initiate a new tumor. Leading approaches to reconcile these different models are that not all cancers follow a CSC hierarchical model [5] and/or that at some stage of the tumor progression the CSC and the clonal model can coexist [6].

The first evidence supporting the hierarchical tumor model and a role for CSCs in tumor formation came from studies on acute myeloid leukemia (AML) [7,8]. Mice receiving cancer cells from AML patients developed leukemia only when given cells that expressed stem cell markers. This suggested that only a limited sub-population of cells in a cancer – the CSCs – can initiate a new cancer and generate diversity that is somewhat parallel to that seen in normal tissues. More evidence supporting the existence of CSCs came from studies of solid tumors affecting the central nervous system and mammary tissue, and, more recently, from a variety of malignancies including liver, thyroid, lung, pancreatic and colon cancers [9,10,11,12,13,14,15].

Despite all the supporting evidence, disputes regarding the actual existence of CSCs in human-grown tumors are also increasing, driven by the fact that the data supporting the CSCs hypothesis come from tumors grown in animal models [16]. Other studies conducted with leukemia and melanoma cells argue that the mouse models commonly employed in CSCs research represent a biased experimental system for the determination of CSC identity and frequency, since they constitute a very selective environment which allows only specific types of tumor cells to survive and proliferate [17,18]. It is evident at this stage that the CSC hypothesis is still subject to ongoing investigation, and that the definition and functions of CSCs are still evolving.

From a therapeutic point of view, the CSC tumor model implies that a complete revision of the traditional anticancer therapies may be necessary. Radiation and chemotherapies mainly target the rapidly multiplying tumor cells that constitute the bulk of the tumor but spare the CSC cells that are mostly dormant. The survival of CSCs allows the tumor to re-grow following treatment. Moreover, like normal stem cells, CSCs express high levels of proteins that allow the CSCs to survive treatment and ultimately contribute to tumor resistance [19,20,21]. Although it seems evident that a therapy that eliminates CSCs is necessary to ensure a complete killing off of the tumor, is still not clear whether that would be enough to prevent recurrence. As mentioned above, tumor cells are very plastic, and it has been experimentally shown in different cancer models that when CSCs are removed from the tumor, part of the remaining non-CSC cells can spontaneously convert into CSCs. This re-establishes an equilibrium between CSCs and non-CSCs. Signals from the normal tissue around the tumor, as well as chemical and radiation treatments, can induce other cancer cells to revert to a stem-like state [22,23]. This complicated picture requires the design of a multi-target approach with the goal of killing CSCs as well as the rest of the tumor cells. Unfortunately, due to the similarities between CSCs and normal healthy stem cells, current therapies that target CSCs are limited in that they may also eliminate normal stem cells. Furthermore, it has been extremely difficult to identify proteins or expressed genes that can be used to specifically identify CSCs. Therefore, current research efforts are focused on ways to identify CSCs and on strategies to induce their differentiation into proliferating cells that can be eliminated by currently available anticancer drugs. Whatever the end result, it is clear that the study and targeting of CSCs represent one of the biggest future challenges of cancer research.

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