Cancer Stem Cells: Exploring the Roots of Cancer
Tumors are composed of a heterogeneous population of cancer cells, characterized by sustained proliferative signaling, evasion of growth suppressors, resistance to cell death signals, acquisition of replicative immortality, induction of angiogenesis, activation of invasion and metastasis, reprogramming of energy metabolism, and evasion of immune destruction. The tumor is perceived as an organ. Like other organs, tumors contain “individual specialized cell types” (cancer cells and non-cancer cells), which cooperate to promote tumorigenesis.

Experimental evidence suggests the entire population of tissues making up organs can be propagated from a single stem cell. Stem cells (like those found in hematopoiesis) possess long life spans, can self-renew, and differentiate into short-lived progenies (red blood cells). Tumors, which have been shown to possess characteristics of organ tissue, also have been shown to contain stem-like cells. They also use the same signal pathways as stem cells to propagate the tumor cells.

Like normal stem cells, cancer stem cells (CSCs) are slow-cycling, can self-renew, and can differentiate to give rise to the heterogeneous tumor. CSCs are identified by markers, including CD133, CD44, CXCR4, and ALDH. CSCs depend on stemness signals secreted from cells in the tumor microenvironment to maintain self-renewal, as well as differentiate into the rest of the heterogeneous tumor cells.
Extensive advances have been made in our understanding of cancer pathogenesis, the mechanisms of disease progression, and disease management. Even with these advancements, metastasis and drug resistance remain major limitations to improving clinical outcomes. Current therapeutic modalities, including chemotherapy and radiation therapy, target mostly rapidly proliferating cells. In contrast, CSCs are slow-cycling and drug-resistant. While effective in reducing tumor size and slowing tumor growth, chemotherapy and radiation therapy also affect the tumor microenvironment. For example, radiation has been shown to induce recruitment of proinflammatory cells to the site of treatment, as well as induce a hypoxic tumor microenvironment, both of which support CSC stemness pathways and eventually tumor progression.
Stem cells interact with their microenvironment (niche) to maintain their stemness potential. The stem cell niche is comprised of a variety of cells, including stromal cells, immune cells, and vascular endothelial cells. These cells secrete factors to create a “fertile soil” for stem cells to self-renew (maintain undifferentiated stem cells) and propagate mature differentiated progenies. Depletion of the niche factors or detachment of stem cell from the niche can lead to differentiation.

Stem cell stemness pathways are highly regulated. For example, the intestinal crypt depends on stemness pathways (especially the Wnt/β-catenin pathway) to maintain epithelial homeostasis. Deregulation of Wnt/β-catenin signaling results in precancerous adenomas. Dysregulation and unrestricted crosstalk between multiple stemness pathways result in CSC pathogenesis. This is the major difference between normal stem cells and CSCs.
The same signal transduction pathways, including Wnt, Hedgehog, Notch, and STAT, that govern normal stem cells are suggested to govern CSC pathogenesis.

In Wnt signaling, Wnt ligands, secreted from stromal cells, bind to Wnt receptors on the cell membrane. This leads to the nuclear translocation of β-catenin. Nuclear β-catenin activates the transcription of "stemness" factors, including the self-renewal genes LRG5 and AXIN2,12 as well as the prosurvival signal survivin.13

STAT3, in a complex with Nanog signaling, is required for the expression of genes involved in the modulation of pluripotency.14 STAT3 hyperactivation has been shown in CSCs compared with non-CSCs or the unfractionated tumor population.15

Activation of Hedgehog signaling leads to modulation of many genes involved in cell proliferation, differentiation, invasion, and survival. Nanog is a direct target of Hedgehog signaling.16

Activation of Notch results in the transcription of protumorigenic proteins, including cyclin D.17 Notch activation has been implicated in epithelial-to-mesenchymal-transition (EMT) and therapy resistance.18 Notch also has been shown to cross-communicate with other pro-oncogenic pathways, including Hedgehog, Wnt, PDGF, TGF-β, PI-3K/AKT, mTOR, and NF-κB signaling.17
CSCs encompass a small percentage of the tumor population. Via stemness signaling, CSCs propagate the tumor population by asymmetric cell division to produce a daughter CSC and a progenitor cell that is capable of expanding into different types of tumor tissue cells.\(^\text{19}\) Experimental evidence from many research groups has suggested that, although current therapeutic regimens affect a significant amount of the tumor cells, there is an enrichment of highly tumorigenic and therapy-resistant CSCs, leading to tumor relapse (recurrence).\(^\text{20,21}\) Furthermore, inflammatory cytokines released by inflammatory cells at primary sites after therapy have been shown to further promote tumor relapse by inducing mesenchymal stem cells to release proangiogenic factors.\(^\text{22}\) In head and neck tumors, the majority of CSCs are located in close proximity to blood vessels and depend on signals secreted from endothelial cells to promote CSC stemness signaling (self-renewal and survival).\(^\text{23}\) This may promote tumor metastasis.
CSCs possess a higher propensity for metastasis and worse prognosis in several cancers, including prostate, lung, and colorectal. EMT may be an important component of these events.

Research in prostate cancer suggests that radiation therapy results in an adherent senescent population, which resumes proliferation after termination of radiation exposure, as well as a nonadherent population. The radio-resistant cells, compared with the non-treated cell population, express pro-EMT characteristics, including SNAIL and CSC markers, including CD133, SOX2, OCT4, and Nanog. The nonadherent therapy-resistant population express the highest levels of EMT and CSC markers.24

A similar phenomenon has been observed in lung cancer after exposure to an epidermal growth factor receptor (EGFR) inhibitor.25

Analysis of peritoneal washings from colorectal cancer patients after curative surgery indicates that higher expression of CSC markers predicted lymph node metastasis, greater tumor stage, and shorter overall survival and peritoneal recurrence-free survival.26
Induction of EMT and survival of circulating tumor cells (CTCs) is dependent on extracellular signal-regulated kinase (ERK) signaling. CTCs, which can contain CSCs, travel to distant sites through the circulatory and lymphatic systems. The presence of CTCs correlate with worse clinical outcomes. A subpopulation of these CTCs may be tumor-initiating CSCs that, upon exiting the circulatory system, can interact with the microenvironment at distant sites to promote tumor metastasis.

Currently, methods of isolating circulating CSCs are under investigation. These CSCs have been shown to possess tumor-initiating properties. Some cancer patients with CSC-positive CTCs have a significantly higher risk of lymph node metastasis, tumor recurrence, and distant metastasis compared with patients with CSC-negative CTCs or patients with no CTCs. Just as CSCs are responsible for the propagation of a tumor at a primary site, CSCs in CTCs may be responsible for propagating tumors at distant sites.
Combining anti-CSC therapy with conventional treatment modalities provides a rational approach to targeting the underlying subpopulation that drives the growth of the entire heterogeneous tumor. This combination would target highly proliferative tumor cells, which make up the bulk of the tumor, and the drug-resistant stem-like cell subpopulation responsible for propagating the entire tumor mass at both the primary and distant sites. This may lead to a decrease in tumor recurrence and metastasis and an improved patient prognosis.4,7
REFERENCES


