Cancer Stem Cells: Implications for Cancer Therapy

ONCOLOGY

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The survival of patients with cancer has improved significantly, primarily because of multidisciplinary care, improved chemotherapeutic agents in both the adjuvant and metastatic settings, the introduction of targeted biologic agents, and the incorporation of palliative care services into the management scheme. However, despite these advances, a

Reviews

Cancer Stem Cells

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significant proportion of patients continue to experience recurrence after adjuvant treatment, and survival associated with stage IV solid tumors still remains low. A primary or acquired resistance to chemotherapeutic and biologic agents is responsible for the failure of many of the agents used to treat patients with a malignancy. This can be explained by the presence of intratumoral heterogeneity and the molecular complexity of many cancers. Factors contributing to intratumoral heterogeneity include genetic mutations, interactions with the microenvironment—and the presence of cancer stem cells. Cancer stem cells have been identified in a number of solid tumors, including breast cancer, brain tumors, lung cancer, colon cancer, and melanoma. Cancer stem cells have the capacity to self-renew, to give rise to progeny that are different from them, and to utilize common signaling pathways. Cancer stem cells may be the source of all the tumor cells present in a malignant tumor, the reason for the resistance to the chemotherapeutic agent used to treat the malignant tumor, and the source of cells that give rise to distant metastases. This review will focus on properties of cancer stem cells; will compare and contrast the cancer stem cell model with the clonal evolution model of tumorigenesis; will discuss the role

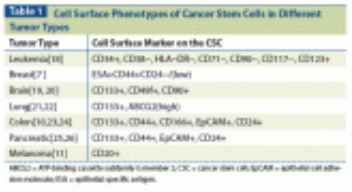

Table 1 Cell Surface Phenotypes of Cancer Stem Cells in Different Tumor Types

Tumor Type	Cell Surface Marker on the CSC
Leukemia[10]	CD34+, CD38−, HLA-DR−, CD71−, CD90−, CD117−, CD123+
Breast[7]	ESA+CD44+CD24−/low
Brain[18, 20]	CD133+, CD49f+, CD90+
Lung[21,22]	CD133+, ABCG2(high)
Colon[10,23,24]	CD133+, CD44+, CD166+, EpCAM+, CD24+
Pancreatic[25,26]	CD133+, CD44+, EpCAM+, CD24+
Melanoma[11]	CD20+

MESO = ATP-binding cassette subfamily G member 2; CSC = cancer stem cell; EpCAM = epithelial cell adhesion molecule; ESA = epithelial-specific antigen.

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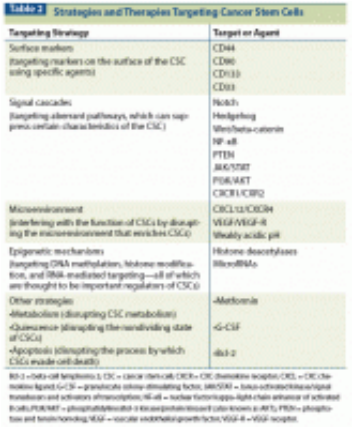

Table 2 Strategies and Therapies Targeting Cancer Stem Cells

Targeting Strategy	Target or Agent
Surface markers (targeting markers on the surface of the CSC using specific agents)	CD44 CD90 CD133 CD33
Signal cascades (targeting aberrant pathways, which can suppress, overlain characteristics of the CSC)	Notch Hedgehog Wnt/beta-catenin NF-κB PTEN JAK/STAT PI3K/AKT CXCR1/CXCR2
Microenvironment (interfering with the function of CSCs by disrupting the microenvironment that enriches CSCs)	CXCL12/CXCR4 VEGF/VEGF-R Weakly acidic pH
Epigenetic mechanisms (targeting DNA methylation, histone modification, and RNA-mediated targeting—all of which are thought to be important regulators of CSCs)	Histone deacetylases MicroRNAs
Other strategies •Metabolism (disrupting CSC metabolism) •Quiescence (disrupting the nondividing state of CSCs) •Apoptosis (disrupting the process by which CSCs evade cell death)	-Metformin -G-CSF -Bcl-2

BCL-2 = B-cell lymphoma 2; CSC = cancer stem cell; CXCR = CXC chemokine receptor; CXCL = CXC chemokine ligand; G-CSF = granulocyte colony-stimulating factor; MAPK/ERK = mitogen-activated protein kinase; NF-κB = nuclear factor kappa-light-chain enhancer of activated B cells; PI3K/AKT = phosphatidylinositol-3-kinase/protein kinase B (also known as AKT); PTEN = phosphatase and tensin homolog; VEGF = vascular endothelial growth factor; VEGF-R = VEGF receptor.

Table 2: Strategies and Therapies Targeting Cancer Stem Cells

review the therapeutic implications and challenges of targeting cancer stem cells, with an assessment of the potential such an approach holds for improving outcomes for patients with cancer.

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Introduction

In the year 2014 an estimated 1,665,540 new cancer cases will occur in the United States, leading to approximately 585,720 deaths.[1] Over the last 2 decades, the combined cancer death rate (deaths per 100,000 population) has been on the decline, from a peak of 215.1 in 1991 to 171.8 in 2010. That translates to

approximately a 20% decline in the death rate, with a reduction of 1,340,400 cancer deaths during this time. Factors contributing to the improved survival of patients with cancer include multidisciplinary care, improved chemotherapeutic agents in both the adjuvant and metastatic setting, the introduction of targeted biologic agents (eg, trastuzumab for breast cancer, imatinib for chronic myeloid leukemia [CML]), and the incorporation of palliative care services in the treatment management scheme.[2,3] However, despite these advances, a significant proportion of patients continue to experience recurrence after adjuvant treatment, and survival associated with stage IV solid tumors still remains low, with cure not a goal.

Over the last few decades, the burning questions have been: why do tumors recur, and why is cure not considered an achievable goal in the metastatic setting? A primary or acquired resistance to chemotherapeutic and biologic agents is responsible for the failure of many of the agents used to treat patients with a malignancy. This can be explained by the presence of intratumoral heterogeneity and the molecular complexity of many cancers, such that while some of the tumor cells perish from exposure to chemotherapy, other cells survive exposure and contribute to disease recurrence and progression.[4] Factors contributing to intratumoral heterogeneity and ultimately acquired resistance to chemotherapeutic and biologic agents include genetic mutations, interactions with the microenvironment—and the presence of cancer stem cells.[4] Cancer stem cells are similar to normal stem cells in that they have the ability to self-renew and differentiate. They differ from normal stem cells in that the mechanisms that normally strictly regulate these processes are deregulated, such that there is continuous expansion and production of aberrantly differentiated progeny.[5]

The first compelling evidence for the presence of cancer stem cells came in 1997, when Bonnet and Dick demonstrated that only CD34+CD38− cells derived from patients with acute myeloid leukemia (AML) could initiate hematopoietic malignancies in nonobese diabetic/severe combined immunodeficient mice.[6] Since then, cancer stem cells have been identified in a number of solid tumors, including but not limited to breast cancer,[7] brain tumors,[8] lung cancer,[9] colon cancer,[10] and melanoma.[11] This review will focus on properties of cancer stem cells; comparison of the cancer stem-cell model with the clonal evolution model; discussion of the role of cancer stem cells in the development of resistance to chemotherapy; and a review of the potential therapeutic implications and challenges of targeting cancer stem cells, with an assessment of the potential to improve outcomes for patients with cancer.

Properties of Stem Cells

Three types of stem cells exist: embryonic stem cells (derived from the first division of a fertilized egg), which eventually give rise to all the cells in the adult organs; germinal stem cells (responsible for reproduction); and somatic stem cells (present in different somatic tissues). Normal stem cells have three distinct and unique properties: (1) they can renew themselves, which allows them to perpetuate themselves and maintain a pool of undifferentiated stem cells; (2) they can differentiate into multiple lineages and thus reconstitute a broad range of functional elements within any given tissue; and (3) they can maintain a balance between self-renewal and differentiation, thereby strictly regulating stem cell number. Multiple pathways are involved in the regulation of normal stem cells. The Notch and Sonic hedgehog pathways have been implicated in the regulation and differentiation of neuronal stem cells.[12] Other pathways typically associated with oncogenesis that have also been implicated in the regulation of stem-cell self-renewal include the octamer-binding transcription factor 4, bone morphogenic protein, Janus kinase, and Wnt signaling pathways.[13]

What makes a cancer stem cell different?

Cancer stem cells comprise a small population of cells within a tumor. They are also known as “tumor-initiating cells” or “tumorigenic cells.” Cancer stem cells and normal stem cells have similar cell surface markers. Like normal stem cells, cancer stem cells have the capacity to self-renew, can give rise to different progeny, and utilize common signaling pathways.[14] They

differ from normal stem cells in that they have tumorigenic activity that enables them to form tumors when transplanted into animals—something normal stem cells cannot do.[15] Cancer stem cells can be the source of: (1) all the tumor cells present in a malignant tumor; (2) resistance to the chemotherapeutic agent used to treat the malignant tumor, thus making them responsible for recurrence; and (3) cells that give rise to distant metastases.

Several assays have been developed to isolate cancer stem cells. The most widely used is based on the presence of specific cell surface makers, and the most common methodology used to identify cell surface markers or intracellular molecules is the fluorescence-activated cell sorting method. Markers such as CD133, CD24, and CD44 are typically identified.[16] Table 1 provides examples of the cell surface phenotypes of cancer stem cells in different tumors. Leukemic stem cells have been shown to display the CD34+CD38− surface marker phenotype, in which the loss of CD38 distinguishes these cells from normal hematopoietic stem cells.[6] Breast cancer stem cells have been shown to display the ESA+CD44+CD24−/(low) surface marker phenotype.[7] However, this finding is not considered sufficient for cancer stem cell identification and is usually combined with results from functional assays such as sphere-forming assays (in which cancer stem cells form spheres or colonies in a serum-free or soft agar medium) or transplantation assays (which utilize the properties of self-renewal and tumor propagation inherent to cancer stem cells). In serial transplantation assays, tumor cells are transplanted into immunocompromised mice. Tumors that grow in these mice are then transplanted into another set of immunocompromised mice in order to exhibit the properties of self-renewal and capacity for tumor formation.[15,17]

The clonal evolution model vs the cancer stem cell model

Two separate and mutually exclusive models have been developed to explain the development of tumors. The clonal evolution model postulates that all cells within a tumor contribute in varying degrees to the maintenance of the tumor.[27] In this model, a number of genetic and epigenetic changes occur over time, with the result that the most aggressive cancer cells are ultimately responsible for driving tumor progression. Furthermore, through a series of genetic mutations, any cancer cell within the tumor can become invasive, lead to the development of metastases, and contribute to resistance to therapies and ultimately to recurrence of disease.

The cancer stem cell model proposes that cancer stem cells, which form a subset of the tumor cells, are ultimately responsible for tumor initiation, progression, and recurrence.[27] Through self-renewal and differentiation, cancer stem cells are responsible for the production of various tumor cells and contribute to tumor heterogeneity. Furthermore, according to this hypothesis, tumor metastases and resistance to therapies directly arise from cancer stem cells.

Both the clonal evolution and the cancer stem cell models have distinct therapeutic implications. In the clonal evolution model, a cure can only be achieved when treatment results in the death of the multiple tumor cell populations that are responsible for tumor progression. In the cancer stem cell model, a cure is only possible when treatment targets the cancer stem cells. For the remainder of this review we will focus on therapeutic strategies designed to target the cancer stem cell.

Role of Cancer Stem Cells in Resistance to Chemotherapy

Cancer stem cells have been implicated in the development of resistance to chemotherapy in a number of malignances. Evidence for this emerged first in the setting of hematologic malignancies[6] and then in other solid tumor types.[7-11]

Hematologic malignancies

Patients with AML are treated with courses of chemotherapy followed by consolidation therapy and autologous or allogeneic hematopoietic stem cell transplantation. Those patients who experience a complete response are still at high risk for recurrence caused by residual cells that survive chemotherapy exposure. Early studies have established that AML cells are hierarchically organized and contain CD34+ cancer stem cells that can sustain serial transplantation and have been implicated in chemotherapy resistance.[6] Van Rhenen et al[28] looked at the association between the presence of CD34+CD38− cancer stem cells and clinical outcome in 92 patients with AML. They found that a high percentage of these cancer stem cells at baseline correlated with a high frequency of minimal residual disease posttreatment and a poor prognosis. Furthermore, the minimal residual disease detected after complete response has been shown to be enriched with CD34+CD38− cancer stem cells, which are subsequently associated with relapse.

[29] These cancer stem cells have also been shown to be resistant to therapy with cytarabine, with the resistant cells successfully engrafted into recipients.[30]

CML, characterized by a translocation between chromosomes 9 and 22 that results in the oncogenic BCR-ABL tyrosine kinase, has been successfully treated with the tyrosine kinase inhibitor imatinib and second-generation inhibitors such as dasatinib and nilotinib. The presence of cancer stem cells in CML has been implicated in recurrence of disease following discontinuation of therapy, even among patients who achieve a long-term remission.[31-33]

Solid tumors

One of the first solid tumors in which the presence of cancer stem cells was demonstrated is breast cancer. Al-Hajj et al[7] demonstrated that CD44+CD24−/(low)Lineage− cells isolated in eight of nine patients with breast cancer had the capacity to form tumors when serially transplanted into immunocompromised mice. They reported that as few as 100 cells with this phenotype were needed to form tumors, while thousands of cells with other phenotypes were unable to form tumors when transplanted. Ginestier et al[34] demonstrated that breast cancer cells with increased aldehyde dehydrogenase activity have stem cell properties and are associated with poor prognosis. Human epidermal growth factor receptor 2 (HER2) has also been shown to be an important regulator of breast cancer stem cells, with HER2 overexpression associated with an increase in the cancer stem cell population and blockade of HER2 associated with a decrease in the cancer stem cell population.[35]

Evidence exists for the presence of cancer stem cells in colorectal cancer, with some phenotypes being CD133+[10] and CD44+/CD166+[23] enriched cancer stem cells. CD133+ enriched cancer stem cells have been shown to be more resistant to fluorouracil and oxaliplatin compared with CD133− cells.[36] Evidence indicates that pancreatic cancer stem cells are enriched with CD133+ and CD44+cMet+ cell surface phenotypes.[25,26] Patient-derived pancreatic xenografts treated with gemcitabine have demonstrated an increased frequency of cancer stem cells, which indicates resistance to the therapeutic agent.[37]

Brain tumors

Singh et al[19] have demonstrated the presence of CD133+ enriched cancer stem

cells in glioblastoma (GBM) tumors. Furthermore, CD133+ cancer stem cells from GBM cell lines have been shown to be resistant to the chemotherapeutic agent temozolomide compared with CD133− cells.[38]

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is there a cancer stem cell?I don't think so.If there is,there should be a ebola stem virus, a flu stem virus,a stem fly.

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