Cancer stem cells (CSCs) are becoming an increasingly greater focus of cancer research, as evidence suggests that they may be integral to tumor formation. Understanding the properties and characteristics of CSCs may lead to improvements in cancer diagnosis, therapy, and outcomes. This Special Edition, *Cancer Stem Cells: Current Perspectives, Future Directions*, distributed by *Oncology Times*, offers insight into the role of CSCs in tumor initiation, progression, and metastasis, as well as the signaling pathways implicated in cancer, with a focus on gastric and gastroesophageal cancers. The potential for inhibition of these signaling pathways is also reviewed.

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Despite advances in chemotherapy, targeted agents, and radiation therapy, the prognosis for patients with advanced cancer has remained poor. Drug resistance, metastasis, and recurrence—even after extended periods of remission—pose persistent challenges to cancer management. A growing body of evidence indicates, however, that a subset of cancer cells, called cancer stem cells (CSCs), may hold a key to controlling cancer and potentially achieving durable clinical responses. Ultimately, patient survival depends on getting rid of these cancer stem cells—the seeds we see in the cancerous tumor after treatment, said Max S. Wicha, MD, Distinguished Professor of Medical Oncology and Director Emeritus at the University of Michigan Comprehensive Cancer Center in Ann Arbor, Michigan.

CSCs Drive Tumorigenesis
Normal stem cells are undifferentiated cells in the body that can self-renew, propagate differentiated cells, and proliferate extensively. Laboratory studies have shown that entire organs can be generated from a single stem cell. These discoveries have fueled interest in stem cell therapy for a wide variety of diseases, including neurological, inflammatory, and endocrine disorders.

CSCs are malignant cancer cells that share the capacity of normal stem cells for self-renewal and proliferation and can differentiate into the heterogeneous population of cancer cells that comprise a malignant tumor. Dr Wicha explained. A common misconception is that all CSCs are malignant cancer cells that arise from normal stem cells, but some CSCs may arise from progenitor cells when a mutation endows these cells with the capacity for self-renewal, normally reserved to stem cells (Figure 1). The CSC model of cancer formation is hierarchical in contrast with the traditional stochastic model (see Models of Carcinogenesis on page 3). A growing body of evidence suggests that CSCs are the drivers not only of tumor initiation and heterogeneity, but of treatment resistance, cancer recurrence, and metastasis.

While the idea that cancers can arise from stem cells goes back about 150 years, it was not supported by experimental evidence until the late 1990s. Bonnet and Dick showed that a small subset of acute myelogenous leukemia (AML) cells were capable of transferring AML into immuno-suppressed mice. The proteins expressed on these cells were similar to those expressed on normal hematopoietic stem cells. A few years later, the role of CSCs in tumorigenesis in solid tumors was supported by the finding that human breast cancers also could be transferred to immuno-suppressed mice by a small tumor-initiating cell subset constituting only about 1% to 5% of the cancer cells.1

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“Do Cancer Stem Cells Hold the Key to Controlling Cancer Growth and Spread?”

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Stem cell development: normal and cancer stem cells
Stem cells develop from a central stem cell that grows and then differentiates to create progenitor and mature cell populations. Normal stem cells have the capacity to self-renew (shown by a curved green arrow), develop into mature tissue (shown by a variety of different color cells), and differentiate. CSCs develop via mutation of normal stem cells or progenitor cells. They go on to grow and differentiate to create primary tumors (the dashed line shows that it is unknown which specific types of progenitor cells are involved in the generation of CSCs). CSCs can self-renew, generate heterogeneous populations of daughter cells, and proliferate, just like normal stem cells.

Figure 1. Stem cell development: normal and cancer stem cells (CSCs). Normal tissues develop from a central stem cell that grows and then differentiates to create progenitor and mature cell populations. Normal stem cells have the capacity to self-renew (shown by a curved green arrow), develop into mature tissue (shown by a variety of different color cells), and differentiate. CSCs develop via mutation of normal stem cells or progenitor cells. They go on to grow and differentiate to create primary tumors (the dashed line shows that it is unknown which specific types of progenitor cells are involved in the generation of CSCs). CSCs can self-renew, generate heterogeneous populations of daughter cells, and proliferate, just like normal stem cells.

Models of Carcinogenesis
The classical model of cancer formation, termed the stochastic model, defines tumor cells as biologically equivalent. Intrinsic factors, such as signaling pathways and levels of transcription factors, and extrinsic factors, such as the microenvironment, host-specific factors, and immune response, result in varied and unpredictable behavior of the tumor cells. Therefore, tumor-initiating activity cannot be assigned to any specific type of cells. Conversely, the hierarchy model proposes that tumors are made up of biologically distinct types of cells with varying functions and behaviors. Tumor growth can only be initiated by a subset of cells known as cancer stem cells (CSCs), which can self-renew and differentiate to non-tumorigenic progeny that comprise the tumor mass (Figure 1).

According to Max S. Wicha, MD, research suggests that both models are correct. “What we know now is that the CSCs themselves can mutate. As cancers develop, the CSC that started the tumor can then mutate and produce a new clone, and at the top of the clone is a CSC. There can be more than one CSC in an individual cancer. Therefore, in a way, the stochastic model and the CSC model are both correct: stem cells mutate and get selected out and each stem cell then generates a clone. Thus, in the middle, the tumor is a mixture of stem cells and multiple clones that come from these tumors.”

By exploring the hierarchy model, the stochastic model can be better understood. Tumor heterogeneity is usually defined in the clinic as tumor shrinkage of at least 50%. The problem with that traditional endpoint is that for the vast majority of cancers, tumor shrinkage does not translate to patients living longer,” Dr Wicha said. An explanation for this may be that tumor regression is a mark of the effect of a treatment on the bulk tumor cell population, rather than the CSCs.12

CSCs tend to be resistant to conventional cancer therapies, similar to the resistance to apoptotic therapies observed in normal stem cells. An issue critical by the finding that human breast cancers also could be transferred to immuno-suppressed mice by a small tumorigenic subset constituting only about 1% to 5% of the cancer cells.1

“We need different clinical endpoints in assessing clinical trials that are designed to target CSCs.” – Dr Wicha

The finding that most cells in cancer tumors are non-tumorigenic has important therapeutic implications, Dr Wicha noted. Cancer treatments that target the non-tumorigenic cells will cause tumor regression; however, if they do not affect the CSCs or their signaling pathways, these cells will persist and potentially regenerate the tumor, resulting in relapse.1 One implication of this finding is that “current evaluation of treatment may be inadequate,” he pointed out.

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to understanding why CSCs are treatment resistant is whether CSCs are discrete populations of cells in cancer or whether non-CSCs can revert to stem cells," Dr Wicha said. Recently, breast cancer stem cells were shown to exist in two states: the epithelial-mesenchymal transition (EMT) state and the mesenchymal-epithelial transition state (MET). In the EMT state, the cells are relatively quiescent but localized at the invasive tumor front, from where they can disseminate via the blood stream to distant micro metastases. In the MET state, the cells are capable of extensive proliferation, growing new tumors. Both cell states are needed to form metastases, and evidence suggests that plasticity of breast CSCs allows them to transition from one state to the other.15

**Stem Cell Divisions Predict Cancer Risk**

The incidence of cancer across different tissues varies widely, but the reason for these differences is unclear.14 For example, the lifetime risk for cancers in the alimentary tract varies by a factor of 24 (0.20% in the small intestine but 4.82% in the large intestine). Such differences cannot be explained fully by environmental or genetic factors, which account for only one-third of the risk variation.10 Recent evidence points to stem cells as the key to understanding why CSCs are treatment resistant (Figure 2).8 CSCs also interact with other components of the cellular microenvironment, such as cytokines, growth factors, and stromal cells (Figure 3).1

"We are finding that CSCs are driven by a limited number of key pathways," Dr Wicha said.8 An expanded understanding of the key signaling pathways of CSCs and of the interactions of these cells with the tumor microenvironment is providing new insights into the mechanisms responsible for the resistance of CSCs to conventional cancer therapies and potential targets for new treatment approaches.8 Evidence has shown that not only are CSCs resistant to chemotherapy and radiation therapy, but that their number can actually be increased by these treatments.15

**Target Selection May Be the Key to Effective Therapy**

During the self-renewal process, normal stem cells interact with their microenvironment (termed the stem cell niche) via tightly regulated signaling pathways. In the early stage of cancer formation, after the stem cell or progenitor cell receives its first mutation, these pathways become dysregulated, allowing the CSCs to expand in an abnormal fashion.14 "We are finding that CSCs are driven by a limited number of key pathways," Dr Wicha said (Figure 2).8 CSCs also interact with other components of the cellular microenvironment, such as cytokines, growth factors, and stromal cells (Figure 3).1

As Dr Wicha explained, evidence shows that cells being killed by chemotherapy secrete inflammatory mediators such as cytokines; some of these are interleukin (IL)-6 and IL-8, which then act to stimulate CSCs. Damage to normal tissue induces a similar response. Injured cells release the same cytokines, signaling the normal stem cells in the tissue to reproduce.16 "This is healthy when it occurs during normal tissue regeneration, but during treatment of cancer with chemotherapy CSC stimulation leads to their increase," he added.

Dr Wicha noted that new approaches to cancer treatment include targeting CSCs and their signaling pathways, such as Notch, Wnt, Hedgehog, and JAK/STAT, which regulate the CSC internal circuitry. Cancer treatments may also target inflammatory cytokines, such as IL-6 and IL-8, which mediate the interaction between CSCs and the tumor microenvironment (Figure 3).4 The blockade of IL-8 receptors as a potential treatment approach has been studied in breast cancer by Dr Wicha’s group and others.17 Targeting some of the pathways involved in CSC self-renewal may not only stop CSCs from reproducing, but also lead to their differentiation into non-stem cells, thereby making them chemotherapy-sensitive," Dr Wicha said. Evidence suggests that when IL-8 receptor blockers are used in combination with chemotherapy, the CSC population decreases to a greater degree than with chemotherapy alone, perhaps because the CSCs are being prompted to differentiate and become sensitive to chemotherapy.17

Regarding the development of new cancer treatment strategies for cancer, it is important to remember that CSCs represent only a small fraction of the tumor cell population, Dr Wicha noted. If these cells are not killed, the tumor will regenerate. Even if the CSCs are destroyed, the non-CSCs that form the bulk of the tumor can, however, still undergo several rounds of cancer cell division leading to spreading of the cancer. Therefore, for the treatment of advanced cancers, the optimal approach is thought to be a combination of a stem-cell targeting agent with a debulking agent that can destroy the large mass of the tumor cells. That debulking agent can be chemotherapy, for instance, because chemotherapy is effective at targeting the bulk cells, while CSCs are resistant to chemotherapy and radiation therapy.14 According to Dr Wicha, "When treating metastatic disease in the adjuvant setting, CSC-targeted therapy alone may be potentially curative. If we knock out the micrometastases, the cancer may not grow back." For this reason, treatment strategies that target CSCs and the mechanisms responsible for the interaction between CSCs and their microenvironment may represent an important approach to improving patient outcomes.16

**CSC Immunotherapy May Improve Outcomes**

New insights into the biology of CSCs and non-tumorigenic cancer cells are providing the rationale for immunologic approaches targeting CSCs. The unique expression profiles and expressed antigens displayed by CSCs and non-stem cancer cells differ. Immunotherapies that target the differentiated cancer cells that form the tumor bulk may not effectively target the antigens expressed by CSCs. In addition, CSCs themselves exhibit heterogeneity.1 Thus, molecular profiling of CSCs and cancer tumors and targeting of immunotherapy at heterogeneous CSC populations “represent one of the most exciting areas in cancer research. Specifically, targeted immunotherapy offers the potential for durable responses in patients with cancers who previously had few therapeu- tic options,” noted Dr Wicha.

CSCs can evade the immune system even more efficiently than the differentiated cells forming the tumor bulk. For example, CSCs express high amounts of programmed death (PD)-1 ligand 1 (PD-L1). The PD1/ PD-L1 pathway (an immune checkpoint) is one of two recognized immunosuppressive pathways that contribute to an immunosuppressive microenvironment that protects cancer cells from immune destruction.18 Thus, a current approach to the treatment of a variety...
of cancers focuses on combinations of such immune checkpoint blocking therapies, other immunotherapies (such as IL-6 or IL-8 inhibitors), and vaccines that target CSCs. The vision for the future of cancer therapy is to base treatment selection on a complete molecular diagnosis of the tumor, including an evaluation of the stem-cell profile of that particular tumor, noted Dr Wicha. From an analysis of the immune infiltrates of the tumor, it also will be possible to know whether the patient is mounting an immune response against the tumor. Dr Wicha believes that cancer treatment will move toward a combination approach—targeting the tumor bulk, CSC populations, and immune components. This will lead to “substantial, rather than merely incremental, gains in treating cancer. Most importantly, this future approach may offer a more durable patient response as opposed to an increase in survival of only 1 or 2 months.”

New Therapies, New Challenges
With new treatments come new challenges. As Dr Wicha explained, “The first challenge is to determine whether an agent that targets CSC pathways will be cytotoxic to normal stem cells, because they use the same pathways. Early trials must test low doses of these agents and escalate them carefully,” he said. “Several phase 1 trials have already shown that most agents targeting CSC pathways can be given effectively with relatively low toxicities and that, based on biopsies performed before and after treatment, the targets are being hit.” Going forward, researchers will analyze whether combining these agents with chemotherapy or immunologic agents will have the potential for increased side effects, such as inducing autoimmunity against the normal stem cells. “These investigations must proceed carefully,” he cautioned.

“The second challenge is the need to rethink the use of traditional endpoints of tumor regression in clinical trials,” Dr Wicha noted. Because CSC-targeting agents do not cause tumor regression, he explained, investigators must work with the United States Food and Drug Administration to determine how to demonstrate conclusively that these agents provide a benefit. “What are the acceptable endpoints?” he asked. “What should we be measuring?” Obviously, phase 1 trials are designed to study potential agents that target CSC signaling alone, with careful monitoring of potential toxicity risks. Phase 2 studies will then assess chemotherapy alone compared with chemotherapy plus an agent targeting a CSC pathway. Potential endpoints in these studies will likely be time to develop new metastases, time to tumor progression, and progression-free or overall survival, rather than tumor regression.

A neoadjuvant trial design that assesses the level of complete pathological response has great appeal for CSC research in a number of tumor types, Dr Wicha said. Complete pathologic response with neoadjuvant therapies is associated with a favorable outcome and has already led to the approval of a new agent to be used as dual anti-HER2 therapy in patients with HER2-positive breast cancer. Another possible endpoint in the neoadjuvant setting is the measurement of residual CSCs after treatment, as the presence of these cells after neoadjuvant therapy has been associated with a poor prognosis.

The other technology receiving increased attention is the isolation of circulating tumor cells. As Dr Wicha explained, circulating tumor cells are highly enriched in stem cell markers in patients with breast cancer. Whereas 1% to 5% of cells are CSCs in primary cancers, studies have shown that closer to 30% to 50% of circulating tumor cells express stem cell markers. Circulating tumor cells may prove useful as biomarkers for patients in clinical trials; isolating and measuring circulating tumor cells may be a way to monitor patients and determine the efficacy of potential treatments. The utility of these assays as predictive of outcomes must be proven in rigorous clinical trials,” Dr Wicha noted, “but this is the kind of research now being explored, as agents that target CSC pathways are increasingly used in the clinical research setting.”

Conclusion
CSCs as potential therapeutic targets may be instrumental in developing therapies that control cancer and allow for the achievement of durable clinical responses in patients. Expanded understanding of the biology of CSCs, their key signaling pathways, molecular diagnosis of tumors, and appropriate clinical trial endpoints will help in the development of agents targeting key signaling pathways.

References
Cancer Stem Cells: Lessons From Gastroesophageal Cancer Biology

Interview with Jaffer A. Ajani, MD
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Gastrointestinal and esophageal cancers are, respectively, the third and sixth most common causes of cancer-related deaths worldwide. During the past several decades, the incidence of these cancers has decreased. In the United States, the incidence has shifted rapidly from esophageal squamous cell carcinoma and distal gastric carcinoma to adenocarcinoma of the esophagus and proximal stomach. In essence, gastric and esophageal cancers are now being seen more commonly at the gastroesophageal junction.

In the United States, gastric cancer is mostly diagnosed in later stages, when survival is at its poorest. Indeed, localized gastric cancer represents only about one quarter of all gastric cancer diagnosed in the United States (Figure 1). "The survival advantage provided by current therapies for patients with regional and metastatic disease is pitifully marginal," Jaffer A. Ajani, MD, commented. Dr Ajani is Professor in the Department of Gastrointestinal Medical Oncology at the University of Texas MD Anderson Cancer Center in Houston. "Our research is now showing that cancer stem cells (CSCs) are central to the lack of success when we treat patients with gastric or esophageal cancer."

CSCs and the Role of the Microenvironment

As defined by the American Association for Cancer Research Workshop on Cancer Stem Cells, a CSC is a cell that has the ability to self-renew and give rise to heterogeneous lineages of cancer cells. Because they have an intrinsic ability to propagate tumor cells, CSCs are also referred to as "tumor-initiating cells" or "tumorigenic cells" (Table 1). The ability of stem cells to self-renew and give rise to multiple cell lineages is termed "stemness."

The microenvironment plays an important role in the support and development of CSCs. Essentially, CSCs exist within a microenvironment consisting of stromal cells, immune cells, neighboring vasculature, and secreted factors that are produced by these cells. These elements create a niche where CSCs can survive and subsequently propagate into the cells that comprise the tumor mass. As such, the niche may be considered to be a regulatory microenvironment where the stem cell-like characteristics of CSCs are nurtured to maintain their self-renewal and differentiation activities. Studies have shown that pathological alterations in normal microenvironments may produce tumor microenvironments that serve as CSC niches.

Tumor Progression and Metastasis

As noted, gastric cancer is usually diagnosed at later stages. This may be because patients often do not exhibit symptoms until their disease has progressed, or their symptoms have been vague and attributed initially to causes other than cancer. "Patients with gastric cancer often have nonspecific symptoms for a long time. It is not unusual for them to see multiple doctors, until finally, when the diagnosis is made, the tumor is well established," Dr Ajani said.

Research is pointing to the migration of CSCs from the primary tumor site as an underlying mechanism of tumor progression and metastasis. The clinical pattern of patients with metastatic disease bears this out, Dr Ajani said. "Often, we can’t find the metastatic tumors in patients who are treated initially with a curative intent," he noted. "When the primary tumor is treated, whether with preoperative therapy or chemotherapy and/or chemoradiation followed by surgery, we observe several phenomena. The primary tumor is often resistant to therapy. We know from our experience, than the more resistant the primary tumor, the more metastatic potential it has. In other words, this aggressive biology is probably related to the number of CSCs (and evolved species of CSCs) present in the primary tumor or volume of the tumor, dictates metastatic potential," he explained. In addition, although it may appear that local treatment has been successful, highly resistant metastatic disease often becomes apparent very quickly.

"One of our biggest problems is that most patients have very advanced tumors when finally seen at our clinic. To me, that signals an older tumor, with many generations of evolved cancer cells and a great deal of resistance to therapy," Dr Ajani said.

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"Treatment resistance is usually due to cross-activation of the HER2 signaling pathway by other pathways, including insulin-like growth factor, c-MET, growth differentiation factor 15, and other members of the EBRB family. Moreover, hyperactivation of downstream HER2 pathway components, such as MAPK and PI3K/AKT, may further contribute to HER2 therapy resistance. There is a need for better targeted therapies," Dr Ajani said.

The molecular events involved in tumorigenesis have been explored to a great extent in many types of cancer. Dr Ajani said, but those involved in gastric and gastroesophageal cancers are not well understood (see The Molecular Side of Gastric Cancer on page 10).

The CSC phenomenon is seen repeatedly in the clinic, Dr Ajani said, "but we are yet to identify a curative therapy or cure anything about it." He described three patterns of response and resistance observed in patients with advanced and metastatic tumors following first-line therapy.

The molecular pattern observed in gastric and gastroesophageal cancer patients is almost a 50% chance they will experience some reduction in tumor volume and improvement in their symptoms for a short time," he said, "but after a few months, the cancer starts to grow." Second-line therapy produces less reduction in tumor volume and for a shorter duration response. This supports some of the preclinical research demonstrating that the CSC population is enriched by cancer treatments, making the tumor more resistant, he added.

A second pattern involves patients whose tumors exhibit primary resistance, according to Dr Ajani. These patients never experience tumor shrinkage even with...
Cancer is a heterogeneous disease with diverse molecular characteristics. Multiple experimental and clinical investigations have implicated a wide range of germline and somatic alterations that drive tumor progression.\(^1\) Recently, the Cancer Genome Atlas Research Network analyzed nearly 300 samples of previously untreated gastric and gastroesophageal cancer and grouped them into four major molecular subtypes:  
- The Epstein-Barr Virus (EBV)-positive group, which made up 9% of gastric cancers. This group displays high prevalence of DNA hypermethylation, including promoter methylation of the tumor suppressor CDKN2A (p16\(^{INK4A}\)) and CDKN2B (p15\(^{INK4B}\)). There is a high incidence of PIK3CA mutations, amplifications of several oncogenes, including ERBB2, and recurrent amplifications of chromosome 8q (leading to overexpression of PD L1/2 and JAK2).\(^1\)
- The microsatellite instability (MSI) group, which made up 22% of gastric cancers. This group is characterized by enrichment for microsatellite instability (MSI), including hypermethylation at the MLH1 promoter. The MSI subgroup exhibits muta- tions in many cancer "hotspots," such as PIK3CA, ERBB3, ERBB2, EGFR, and overexpresses mitotic pathway components.\(^2\)
- The genomically stable subgroup, which made up 20% of gastric cancers. This group exhibited mutations in CDH1, a protein important in cell motility and the STAT3 signaling pathway.\(^2\)
- The high chromosomal instability (CIN) group, which made up about 50% of gastric cancers. This subgroup is concentrated at the gastroesophageal junction.\(^3\) The CIN group exhibited hyper-activation of EGFR and other RAS-driven receptor tyrosine kinases, mutation of the tumor suppressor TP53, and high levels of aneuploidy.\(^4\) Chromosomal instability has been shown to be prevalent in several solid tumors, including those of the head and neck, testes, lung, and liver, as well as in gastric and gastroesophageal cancers. Fewer CINs are seen in melanoma, and even fewer in Wilms' tumors.\(^5\)

While these subtypes are informative, they do not capture the complexity of gastric cancer, particularly within the context of microenvironmental factors. The microenvironment plays a crucial role in chemoradiation therapy resistance. The inflammatory microenvironment components, such as fibroblasts, lymphocytes, mast cells, and macrophages, may support transformation of gastric stem cells to cancer stem cells.\(^6\)

The inner lining of the stomach is organized into a crypt-like structure, containing normal stem cells at the bottom, which is similar to that seen in the inner intestinal lining, but not as deep, Dr Ajani explained (Figure 2).\(^7\) Like other stem cells, gastric stem cells self-renew and produce the remaining components of the mucosa. Studies have shown that these stem cells depend on the Wnt/β-catenin pathway to maintain the number of non-stem- and non-muscosa cells. Dr Ajani noted that the Wnt/β-catenin pathway is important for the embryonic development of stomach, stem mucosa cells as well. These muscosa cells begin to form precancerous muscosa cells when the inhibiting component of the Wnt/β-catenin pathway, called adenomous polyposis coli (APC), is removed from the stem cells.\(^8\) This suggests that CSCs may be involved in the initiation and progression of gastric cancer, he said.

Other stemness signaling pathways have been implicated in esophageal cancer. The Hedgehog (Hh) pathway, for example, is transiently upregulated in progenitor cells to induce proliferation after tissue injury. These stem cells progenitor are usually quiescent and return to this state after tissue regeneration via tight regulation of the Hh signaling pathway. Chemoradiation-resistant esophageal cancer has been shown to induce the Hh stemness signal pathway after treatment. Blockade of the Hh pathway components results in reversal of therapy resistance. This suggests that these tumors may be activating this regener- ative signaling pathway to support tumor regrowth after injury or chemoradiation.\(^9\) A similar phenomenon was observed in gastric cancer in which chemotherapy-resistant cells exhibited increased CSC properties, along with an increase in the CSC marker BMI1. Depletion of BMI1 resulted in therapy sensitization.\(^10\)

Chemoradiotherapy resistance is also associated with increased levels of the CSC marker ALDH1. In research conducted by Dr Ajani’s group, expression of ALDH1 after chemo- radiation therapy correlated directly with worse clinical response.\(^10\) Dr Ajani added that the ALDH1 data suggests that CSCs may play an important role in chemoradiation therapy resistance.

“Chromosomal instability-related cancers are more common in organs, such as the lung, stomach, esophagus, head and neck, and skin, which are exposed to external factors,” when they become cancerous, it’s because these malignancies are all carcinogen- dependent and they have a large number of DNA alterations. On the other hand, pediatric cancers and leukemias are more genetically driven and have very few alterations.” – Dr Ajani

CSGs have been shown to play a role in gastric and gastroesophageal cancer metastasis, too. Helicobacter pylori infection has been shown to increase expression of epithelial-mesenchymal transition (EMT) factors in some tumors.\(^11\) This suggests that these tumors may be activating this regenerative signaling pathway to support tumor regrowth after injury or chemoradiation.
A mutation that is driving a cancer sometimes is also driving the CSC. A good example is human epidermal growth factor receptor 2 (HER2) in human breast cancer. HER2 is a very potent driver of breast CSCs, and we think that’s why HER2-targeted therapies have been so successful. However, in some epithelial growth factor receptor (EGFR) appears to be important, the benefit of EGFR inhibitor therapies appears to be short-lived. This may be because we’re see cancers that are resistant to these therapies, but also because the stem cells in those tumors don’t depend on HER2 signaling but rather different pathways.

Dr A: Another aspect to consider is that if we can target CSCs effectively, we may reduce the tumor burden in patients. We may not be able to eradicate the tumor, but we can reduce the tumor bulk. A tumor with fewer stem cells could become indolent. That’s what we hope we can do. Do you think that all cancers will be shown to have CSCs as the key player? Dr W: I think they do play a role in all types of cancers; however, the frequency of cells that are stem-like varies tremendously between different cancers. At one end of the spectrum are hematologic malignancies, where it looks like maybe 1 of 1,000 or 1 of 10,000 cells may be a CSC. The tumors that probably have the highest percentage of CSCs are melanomas. All tumors probably have CSCs within, but to understand these cells we must understand not only the biology of the cell but how it relates to the microenvironment, including the immune system, in our patients.

Dr A: The short answer to that question is yes; many researchers believe cancer originates in the stem cells and there is a nice explanation for that. In a cell with stem cell properties, damaging the deoxyribonucleic acid (DNA) could cause the cell to become malignant. However, the DNA is damaged in a cancer stem cell, the cell dies because it has a limited number of life cycles. If, for example, DNA damage occurs in 100 cells but only 1 of them is a stem cell, that cell will survive with the DNA damage and eventually become more dominant and become cancerous.

Dr W: Practicing oncologists will start seeing more clinical trials of CSCs and immunotherapies. The key is to follow very closely the results of these clinical trials because oncology is moving at a quicker pace than we’ve ever seen before. I think we’re going to see advances in the CSC area, with the potential for achieving much more durable responses. I would also encourage the practicing oncologist to participate in these trials as members of cooperative groups.

Understanding CSCs may help us to develop new approaches to cancer prevention. Some interventions, like weight reduction, diet, and exercise, may affect stem cells through inflammatory mediators, like interleukin (IL)-6 and IL-8. We know that IL-6 is an important driver of breast CSCs. Women with breast cancer who either lose weight or undergo an active exercise intervention program lower their levels of inflammatory cytokines, such as IL-6, by 50%. Dormancy of cancers is also an issue. In diseases like estrogen receptor–positive breast cancer, cancers can recur after 15 or even 20 years, and molecular analyses are able to show that the recurrent cancers share almost all the same mutations as the original cancers—that they’re actually the same cancer. How did this happen? We think that these are dormant CSCs. Normal stem cells can sit for long periods and become active only

Cancer Stem Cells: Where Are We and Where We’re Going

Max S. Wicha, MD, and Jafer A. Ajani, MD

Why is the concept of targeting CSCs so attractive?

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Do you think that all cancers will be shown to have CSCs as the key player?

Dr W: I think they do play a role in all types of cancers; however, the frequency of cells that are stem-like varies tremendously between different cancers. At one end of the spectrum are hematologic malignancies, where it looks like maybe 1 of 1,000 or 1 of 10,000 cells may be a CSC. The tumors that probably have the highest percentage of CSCs are melanomas. All tumors probably have CSCs within, but to understand these cells we must understand not only the biology of the cell but how it relates to the microenvironment, including the immune system, in our patients.

Dr A: The short answer to that question is yes; many researchers believe cancer originates in the stem cells and there is a nice explanation for that. In a cell with stem cell properties, damaging the deoxyribonucleic acid (DNA) could cause the cell to become malignant. However, the DNA is damaged in a cancer stem cell, the cell dies because it has a limited number of life cycles. If, for example, DNA damage occurs in 100 cells but only 1 of them is a stem cell, that cell will survive with the DNA damage and eventually become more dominant and become cancerous.

What should practicing oncologists know today about CSCs?

5. Xu ZY, Tang JN, Xie HX, et al. 5-Fluorouracil chemotherapy of advanced gastric or gastroesophageal cancer remains one of the most difficult challenges in clinical practice. Research that improves our understanding of these characteristics may ultimately lead to depletion of CSCs in the tumors.
13. Pasegul E, Jamieson CHM, Allison L, Weissman IL. Normal and leukemic hematopoiesis: leukemias as stem cell disorders or a transposition of stem cell characteristics? Proc Natl Acad Sci USA. 2003;100(10 suppl); 11842-11849.
Dr Ajani: Oncologists in the community need to be aware of the ramifications of treating stem cells and non–stem cells. Certain cancers behave like an organ. For example, when skin is injured, normal adult stem cells are animated and cause the skin to heal. They repopulate and maintain the skin. The same phenomenon occurs with cancer. When CSCs are injured by chemotherapy, they will also automatically repopulate. Further, in patients with colon cancer, it has been shown that if all the CSCs are killed, some of the non–stem bulk tumor cells will reformulate and transform into CSCs.

Most clinicians tend to focus on the non–stem cells when treating cancer. We use cytotoxic drugs against this proliferative group of cells and sometimes we have success, but most of the time they produce only a transient effect. Treatment success will occur when CSCs and non–stem bulk tumor cells are treated in unison. That is where we need to go.

To learn more about cancer stem cells, visit: www.bostonbiomedical.com or scan
Despite advancements in treatment modalities, many patients with cancer experience tumor recurrence and metastasis at regional or distant sites. Evolving understanding of tumor biology has led to the hypothesis that tumors possess a stem cell-like subpopulation known as cancer stem cells (CSCs), which may be involved in driving pathogenesis and tumor propagation.

This supplement updates clinicians on the accumulated evidence characterizing the role of CSCs in tumor initiation, heterogeneity, therapy resistance, recurrence and metastasis, and the potential for effectively treating patients by targeting these cells.

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