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# CANCER STEM CELLS

Cancer stem cells fuel tumor growth, spread, and recurrence by evading standard treatments. Understanding them may unlock the next frontier in cancer therapy.

Paul E. Marik, MD, FCCM, FCCP
Justus R. Hope, MD


**Please note: This is a complementary guide on cancer stem cells (CSCs) and repurposed drugs and natural compounds that may target CSCs, potentially improving cancer treatments and outcomes. The full guide, 'Cancer Care: The Role of Repurposed Drugs and Metabolic Interventions in Treating Cancer,' and all scientific references, can be found here: imahealth.org/research/cancer-care**

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# Cancer Stem Cells

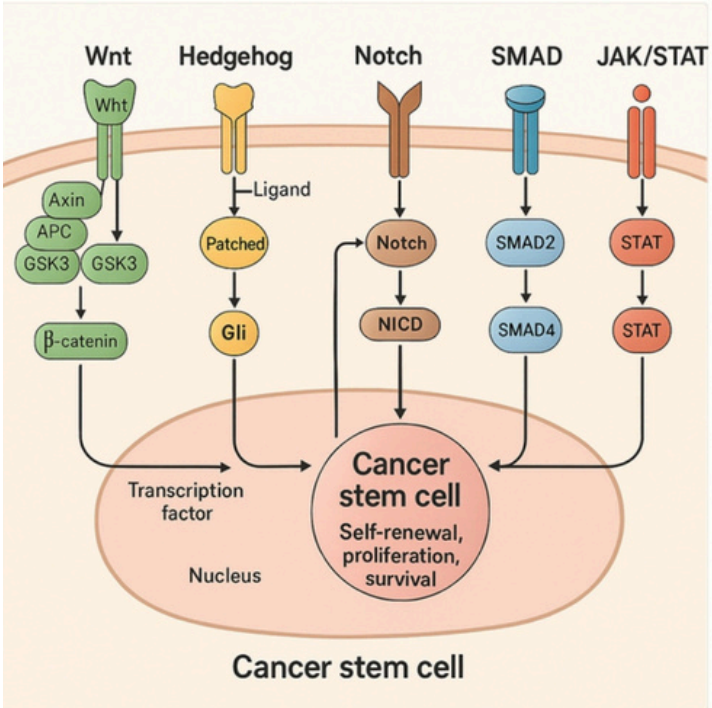
Cancer stem cells (CSCs) are a subset of cancer cells that exhibit characteristics similar to those of normal stem cells, including self-renewal and the ability to differentiate into various cell types within a tumor. These cells are believed to drive tumor initiation, progression, metastasis, and recurrence due to their ability to evade conventional treatments and regenerate tumors. The cell of origin of CSCs is unknown and widely debated. It is postulated that tissue-resident stem cells (TRSCs) transform into CSCs through a combination of genetic mutations, epigenetic changes, and microenvironmental interactions.

## Biochemical Pathways Involved in CSCs

Several key signaling pathways (see Figure 1) are involved in the regulation and maintenance of CSCs, including:

**Wnt/β-catenin pathway**: Crucial for CSC self-renewal and differentiation
**Hedgehog pathway**: Involved in CSC proliferation, self-renewal, and tumorigenicity
**Notch pathway**: Regulates CSC replication, survival, and differentiation
**TGF-β/SMAD pathway**: Promotes CSC self-renewal, migration, and invasion
**JAK/STAT pathway**: Contributes to CSC growth and sustained inflammation in the tumor microenvironment

## Figure 1. Cancer stem cell pathways



## CSC Metabolic Flexibility

CSCs exhibit metabolic flexibility, utilizing both glycolysis and oxidative phosphorylation (OXPHOS), depending on tumor type, microenvironment, and genetic factors. While aerobic glycolysis (the Warburg effect) is common in many cancers, CSCs often retain functional mitochondrial OXPHOS and can switch between these pathways to meet energy demands and survive under stress.

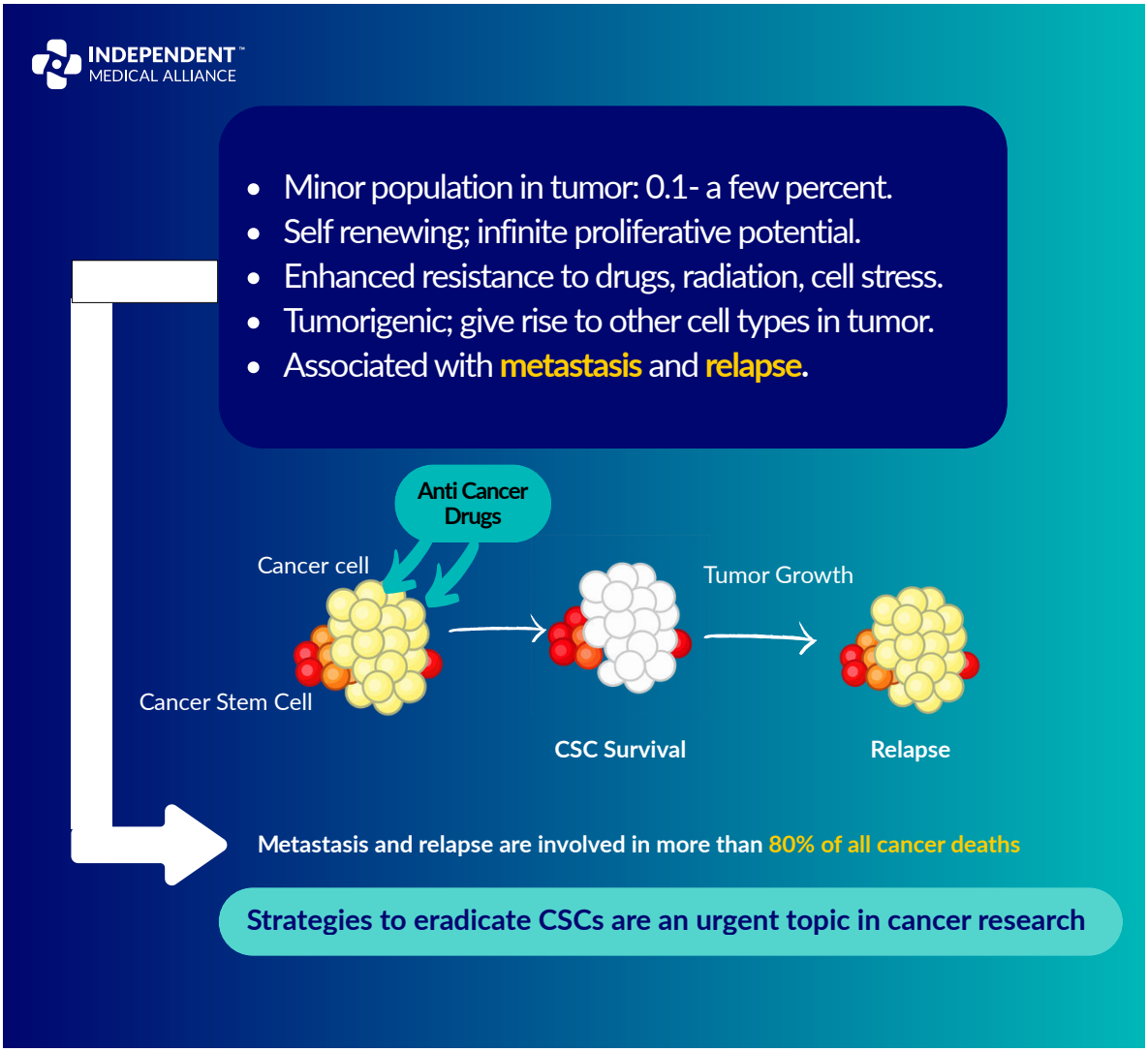
## Effects of Chemotherapy and Radiation Therapy on CSCs

Conventional chemotherapy and radiation therapy primarily target rapidly dividing cells, which form the bulk of a tumor. However, because CSCs constitute only a small fraction of the tumor, their quiescent nature and enhanced resistance mechanisms often allow them to evade treatment. This can lead to tumor recurrence, as CSCs are capable of regenerating the tumor. More concerning, some chemotherapy drugs and certain forms of radiation therapy may actually activate CSCs (see Tables 1 and 2).

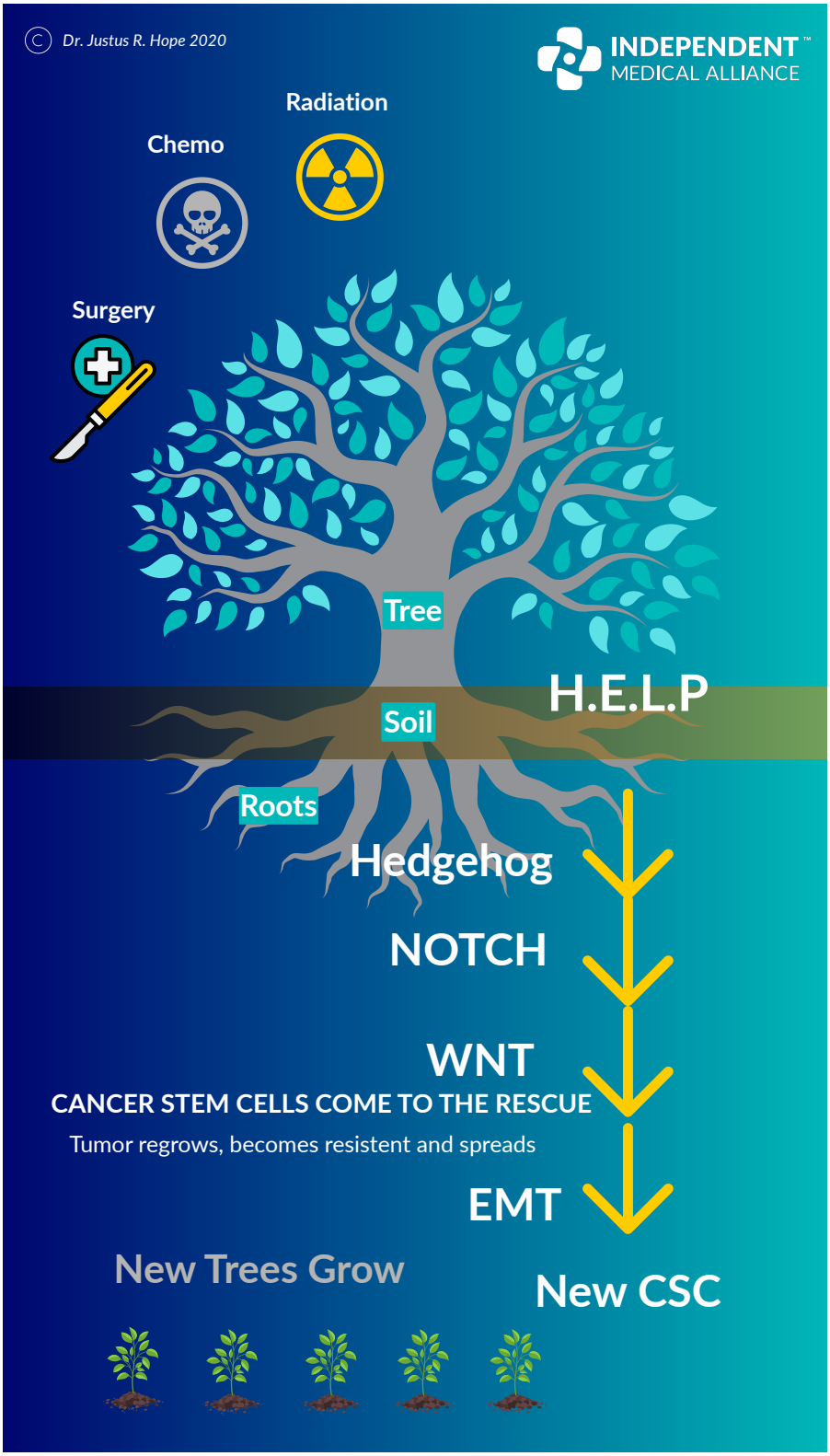
The clinical consequences of CSC resistance—including relapse and metastasis—are illustrated in Figure 2.

Figure 3 provides a visual analogy of how CSCs (like the roots of a tree) survive chemotherapy, radiation, and surgery, leading to relapse and continued tumor growth.

# Figure 2. Characteristics of cancer stem cells (CSCs)



## Figure 3. Cancer stem cells: Visual analogy of resistance and regrowth.



# Why Are CSCs Resistant to Chemotherapy?

CSCs resist chemotherapy through multiple interconnected biological mechanisms that allow them to survive treatment and drive tumor relapse. These mechanisms include both intrinsic adaptations and interactions with the tumor microenvironment (TME), as outlined below:

**1. Intrinsic Resistance Mechanisms**

- **Drug efflux pumps:** CSCs overexpress ATP-binding cassette (ABC) transporters such as ABCB1 and ABCG2, which actively pump chemotherapeutic agents out of the cell. This reduces intracellular drug accumulation and contributes to the multidrug resistance (MDR) phenotype—a hallmark of CSCs.
- **Quiescence (dormancy):** CSCs often enter a slow-cycling or nondividing state, allowing them to evade therapies that target rapidly proliferating cells. For example, glioblastoma CSCs survive temozolomide through phenotypic interconversion between dormant and active states.
- **Enhanced DNA repair:** CSCs exhibit upregulation of DNA damage response pathways, including ATM/ATR kinases and CHK1/CHK2 checkpoints. This enables efficient repair of DNA damage caused by chemotherapy or radiation.

**Anti-apoptotic signaling:** CSCs overexpress anti-apoptotic proteins such as BCL-2 while suppressing pro-apoptotic signals, thereby enabling resistance to chemotherapy-induced cell death.

**2. Extrinsic Resistance Mechanisms**

- **Tumor microenvironment (TME) support:** The TME—comprising adipocytes, fibroblasts, and immune cells—secretes growth factors (e.g., VEGF, FGF) and cytokines that promote CSC survival and stemness. For example, VEGF-NRP1 signaling in glioblastoma enriches chemoresistant CSCs following bevacizumab treatment.
- **Hypoxia:** CSCs thrive in hypoxic niches, where hypoxia-inducible factors (HIFs) are activated and promote stemness while upregulating drug efflux pumps.
- **Epithelial-mesenchymal transition (EMT):** EMT enhances CSC plasticity, invasiveness, and resistance by upregulating stemness markers (e.g., CD44, ALDH1) and survival pathways like Wnt/β-catenin and Hedgehog. For instance, Wnt activation in breast CSCs increases ABCB1 expression.

**3. Signaling Pathways Driving Resistance**

CSCs hijack key developmental pathways to maintain chemoresistance:

- **Hedgehog:** Promotes survival in glioblastoma and colorectal CSCs
- **Wnt/β-catenin:** Upregulated in colorectal and breast CSCs; linked to 5-fluorouracil resistance
- **Hippo-YAP/TAZ:** Sustains stemness in breast cancer and cooperates with Wnt signaling

# Table 1. Cancer stem cell activation by chemotherapeutic agents

| Rank | Chemotherapeutic Agent | CSC Stimulation Level | Key Affected Pathways | Evidence Quality |
|---|---|---|---|---|
| 1 | 5-Flourouracil (5-FU) | Substantially stimulating | WNT/β-catenin, PI3K/AKT, c-Yes/YAP | Strong |
| 2 | Paclitaxel | Moderately to substantially stimulating | Nrf2, EGFR, IL-6 | Strong |
| 3 | Docetaxel | Moderately stimulating | Multiple pathways, similar to paclitaxel | Moderate |
| 4 | Oxaliplatin | Mildly to moderately stimulating | WNT, PI3K/AKT (often with 5-FU) | Moderate |
| 5 | Gemcitabine | Mildly stimulating | Nrf2 pathway | Limited |
| 6 | Cisplatin | Mildly stimulating | Multiple pathways | Limited |
| 7 | Cabazitaxel | Mildly stimulating | Similar to other taxanes | Limited |
| 8 | Doxorubicin | Minimally to mildly stimulating | Multiple pathways | Limited |

# Table 2. CSC activation by radiotherapy

| Rank | Therapy | Full Name | CSC Stimulating Effect | Key Mechanisms |
|---|---|---|---|---|
| 1 | EBRT | External Beam Radiation Therapy | Highest | Induces EMT, promotes non-stem cancer cell conversion to CSCs, activates survival pathways |
| 2 | IMRT | Intensity-Modulated Radiation Therapy | High | Similar to EBRT, but with more conformal dose distribution; still capable of inducing CSC phenotype |
| 3 | VMAT | Volumetric Modulated Arc Therapy | High | Arc-based version of IMRT with similar biological effects on CSC stimulation |
| 4 | APBI | Accelerated Partial Breast Irradiation | Moderate-High | Localized treatment with photon radiation that may still induce CSC phenotypes in treatment area |
| 5 | IGRT | Image-Guided Radiation Therapy | Moderate | Primarily improves targeting accuracy rather than altering biological effects |
| 6 | SBRT | Stereotactic Body Radiation Therapy | Moderate-Low | Higher ablative doses may reduce CSC stimulation compared to conventional fractionation |
| 7 | PBT | Proton Beam Radiation Therapy | Low | Generate more ROS and DNA damage in CSCs, reduces CSC survival and self-renewal |

# Repurposed Drugs Inhibiting CSCs

Several repurposed drugs and natural compounds have been found to inhibit CSCs through various signaling and metabolic pathways (see Table 3):

- **Ivermectin:** Known for its antiparasitic properties, ivermectin has shown potential to inhibit CSCs by targeting various signaling pathways.
- **Curcumin:** A compound in turmeric with anti-inflammatory and anticancer properties; it inhibits CSCs through pathways such as Wnt/β-catenin.
- **Mebendazole:** An antiparasitic drug explored for its anticancer effects, including targeting CSCs.
- **EGCG (epigallocatechin gallate):** A polyphenol most abundant in green tea; it inhibits CSCs by modulating signaling pathways such as Wnt and Notch.
- **Doxycycline**: An antibiotic studied for its potential to inhibit CSCs by targeting specific pathways.
- **Metformin**: Commonly used to treat diabetes, metformin has been investigated for anticancer effects, including targeting CSCs via metabolic pathways.
- **Vitamin D**: Known for its role in bone health, vitamin D has been studied for its potential to inhibit CSCs by modulating signaling pathways.
- **Sulforaphane**: Found in cruciferous vegetables, sulforaphane has shown potential to inhibit CSCs through various mechanisms.
- **Resveratrol**: A polyphenol found in grapes, resveratrol has anticancer properties and inhibits CSCs by targeting multiple pathways.

These compounds offer promising avenues for developing targeted therapies against CSCs, potentially improving cancer treatment outcomes by reducing recurrence and metastasis.

## Table 3. Repurposed agents active against CSCs and pathways blocked

| Rank | Compound | Pathways Blocked | Safety |
|---|---|---|---|
| 1 | Ivermectin | Wnt, Hedgehog, Notch, NFkB, STAT3, PI3K/AKT | Safe |
| 2 | Curcumin | Wnt, Hedgehog, Notch, NFkB, STAT3, TGF-β, | Safe |
| 3 | Sulforaphane | Wnt, Hedgehog, NFkB, STAT3 | Safe |
| 4 | Doxycycline | Wnt, Hedgehog, Notch | Safe |
| 5 | EGCG | Wnt, STAT3, NFkB, Notch, PI3K/AKT | Safe |
| 6 | Resveratrol | NFkB, STAT3, TGF-β, PI3K/AKT | Safe |
| 7 | Omega-3 (DHA) | STATS, JAK-STAT, NFkB, Wnt | Extremely Safe |
| 8 | Mebendazole | Hedgehog | Safe |
| 9 | Metformin | PI3K/AKT | Extremely Safe |
| 10 | Vitamin D | Notch, Hedgehog | Extremely Safe |

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