Targeting Cancer Stem Cells with Evolutionary Therapies

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Abstract

Cancer is a genetic disease. Normal cells reject growth-controlling signals and develop into tumors, which ultimately cause the organism to be destroyed, due to inherited or somatic changes in DNA. A study of cancer stem cells, which are now thought to be the cause of cancer, their role in carcinogenesis, and their implications for the creation of potential future cancer treatment techniques follows recent advancements in the use of stem cells in cancer therapy. Cancer stem cells (CSCs) are a subset of tumor cells that have the ability to differentiate and self-renew, just like stem cells. The self-renewal mechanism of stem cells may fail, leading to the creation of tumors, and the target cells that undergo malignant transformation may be stem cells. Acute myeloid leukemia and a variety of solid tumors, such as those of the breast, brain, lung, prostate, testis, ovary, colon, skin, and liver, have been reported to include these cells. The CSC theory explains the inefficiency of traditional cancer treatments in addition to the problems of tumor initiation, growth, metastasis, and recurrence.

Keywords: Concrete tumors, Malignant breast cancer, Cancerous prostate stem cells, and Carcinoma stem cells (CSCs)

Cite this Article as: Mujahid A, Hanif A, Saleem A, Fatima SK, Fatima W, Abbas M, Tariq A, Bibi A, Saleem H and Laiba, 2025. Targeting cancer stem cells with evolutionary therapies. In: García-Rubio VG, Alvi MA, Saeed Z and Ahmad M (eds), Foundations of Holistic Healing: Complementary and Alternative Medicine. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 274-280. https://doi.org/10.47278/book.HH/2025.483

A Publication of Unique Scientific Publishers

Chapter No: 25-038

Received: 03-Feb-2025
Revised: 26-March-2025
Accepted: 13-May-2025

Introduction

From the start of the 21st century, the idea of cancer stem cells, or CSCs, has piqued the imagination of scientists. Notably, this year celebrates the 20th anniversary of the first experimental proof of the existence of CSCs (Fulawkaet al., 2014).

The ability of CSCs, or cancer stem cells, which Bonnet and Dick first identified in 1997 in the diagnosis of malignant severe leukemia (AML), to self-renewal and specialize into several cell types has been shown to make them similar to normal stem cells. The study demonstrated that AML in mice can be caused by AML CSCs with the phenotype CD34+ CD38−, which comprise 0.1–1% of malignancies. CSCs have a significant role in cancer treatment resistance to chemotherapy and radiation, according to additional study. Another major problem is that they are more likely to spread (Kusoglu and Avci et al., 2019). A serious threat to human life is cancer, a chronic sickness. Many methods have been developed to treat cancer, including targeted treatment, chemotherapy, radiation, and surgery. All of these treatments have contributed to a constant incidence rate of cancer in women and a slight drop in the cancer death rate in men during the last ten years (2006–2015 and 2007–2016). However, only certain malignant tumors respond well to conventional cancer therapy techniques. The main reasons why cancer treatment fails are metastasis, recurrence, heterogeneity, radiation and chemotherapy resistance, and immune surveillance evasion.All of these problems could be explained by the characteristics of cancer stem cells (Yang at el., 2020).

Concept of Cancer Stem Cells

Tumorigenesis is directly caused by CSCs' potent capacity for self-renewal. CSCs have the ability to symmetrically split into one daughter cell or two CSCs. In order to excessively enhance cell development and finally promote carcinoma formation, CSCs divide symmetrically. Mice with severe combination immunodeficiency disease (SCID) were given CSCs obtained from the initial tumor tissue, which subsequently developed into new tumors (Chen et al., 2011). A number of regulatory signaling pathways that are important in the self-renewal process, including the Notch as well, Acoustic Hedgehog (Hh), and Wnt as well pathways, are also shared by CSCs and normal stem cells. Furthermore, PTEN and the polycomb family are two more signaling molecules that are crucial in controlling the formation of CSCs. The key to comprehending carcinogenesis is the control of CSC self-renewal. Treatment for cancer will have a clear focus thanks to these findings (Dick et al., 2008). Cells having CSC capabilities are also commonly referred to as "tumor-initiating cells." Regarding the cells they refer to, both phrases have the potential to and do generate misunderstandings. As implied by the term CSC, they might be created from healthy stem cells that pick up the genetic hits necessary for malignant transformation. The phrase "tumor-initiating cell" more correctly describes the available experimental evidence, even though it suggests that the tumor-initiating cell is the actual cell from which the tumor originally formed. This is probably not the case because it is well established that the population of tumor-initiating cells, or CSCs, can shift as the disease worsens (Vermeulen et al., 2008).

Cancer Stem Cells and Intratumoral Heterogeneity

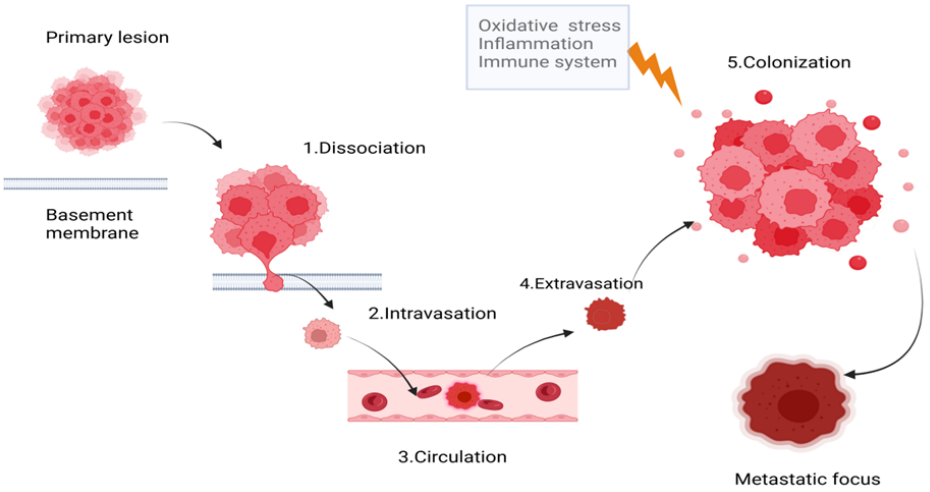
Tumor tissue diversity is deeply associated to the collapse of traditional anticancer treatments. Tumors often encompass of genetically copies of cancerous cells, which established in retort to selection pressure from the tumor microenvironment. In genetically identical tumor cells the diversity occurred due to the variation in gene expression pattern. Intratumoral diversity comes from the combination of functional and genetic variation, making it inherently complex. Normal tissue consists of distinct cell types derived from stem cells, developing hierarchically through epigenetically regulated gene expression. Similarly, tumor also shows the similar cellular hierarchy with cancer stem cells having high tumorigenic and producing progenitor and differentiated cells. Before the CSC theory, tumor diversity is considered random genetic mutation. Tumor diversity is now considered to result from the combined contributions of both genetic and epigenetic mechanisms acting in parallel (Fisher et al., 2013; Gerlinger et al., 2012; Nguyen et al., 2012; Easwaran et al., 2014).

Cancer stem cells have the resistance to redox stress shows "robustness", have the ability of efficient DNA repair , adaptability to microenvironment, metabolic reprogramming ,and drug release via ATP-binding cartridge transporters. These traits contribute in MRD, CSC-enriched lesion that sustain therapy and leads to metastasis and relapse. Chemotherapy-induced MRD influence CSC enrichment through mechanism such as metabolic reprograming or signals from apoptotic non-CSCs. Increased CSC markers after chemotherapy in various cancers highlight their importance in predicting treatment outcomes and prognosis(Ishimoto et al., 2011; Wu et al., 2015; Maugeri-Saccà et al., 2012; Skvortsov et al., 2015; Ishimoto et al., 2010; Yoshida and Saya, 2014; Weinberg et al., 2010; Saga et al., 2014; Dean, 2009; Meads et al., 2009; Creighton et al., 2009; Viale et al., 2014).

The Niche, a Favorable Microenvironment for CSCs

Normal tissue stem cells are commonly reside in the microenvironment or “niches” made up of different type of cells, ECM, and many other growth factors. Likely, CNCs are maintained and growth in niches having endothelial cells, osteoblasts, hyaluronic acid and EMC molecules. Cancer-associated fibroblasts, and undifferentiated mesenchymal stem cells and macrophages associated with tumor or monocytes within the tumor interstitium act as microenviornment for cancer stem cells by secreting different cytokines like epidermal angiogenic molecules, hepatocyte angiogenic molecules,transforming growth factor –β,along with mediators for the inflammation such as tumor necrotic tissues factor-α and lymphokine like IL-1β and IL-6. This niche activates the NF-kB signaling pathway, which not supports growth but maintain CSCs to take part in metastasis and recurrence. For instance, Melanocytic stem cells located in sweat gland secretory portion in the volar skin helps in development of acral melanoma, which contribute in multiplication of oncogenic encoding cyclin-D1.It represents that CSCs emerge from non-pathological tissues and collabrate their microenviornment(Sato et al., 2011; Rabbani et al., 2011; Guerrouahen et al., 2011;De Veirman et al., 2014; Jinushi et al., 2012; Hoesel & Schmid, 2013a).

The idea of the microenvironment is crucial in understanding the “seed and soil” idea of infiltration of tumor, suggested by Paget, which present the site where the primary tumor determines the metastasis of cancer cells within bloodstream to a pre-metastatic niche. For example, carcinogenic cells secrete PTHrP, influencing bone resorption and formation and help in entering the cancer cells in the bone marrow. The phenomenon where metastasized circulating tumor cell CTCs return to the tumor development area is known as “tumor self-seeding” , Cancer stem cells not only spread to distant sites but also able to reach to its origin, as the primary tumor sites provide the acquainted niche and support factors. CTCs have the ability to modify the niche to favor tumor formation in both the primary site and distant site (organ). For example, self-seeding is performed by the high expression of MMP-1, collagenase-1etc (Ribatti et al., 2006; Shiozawa et al., 2011; Yoneda & Hiraga, 2005;S un et al., 2005; Norton & Massagué, 2006; Comen et al., 2011; Kim et al., 2009). Figure 1 elaborates secondary tumor spread depend on cancer stem cell theory, involves several steps: cancer cells detach from the tumor development area (1) enters into bloodstream (2) circulating as CTCs (3) exit into distant tissues (4) settle down in pre-metastatic niche to form metastasis (5) Success of metastasis depends on whether the niche support CTCs.



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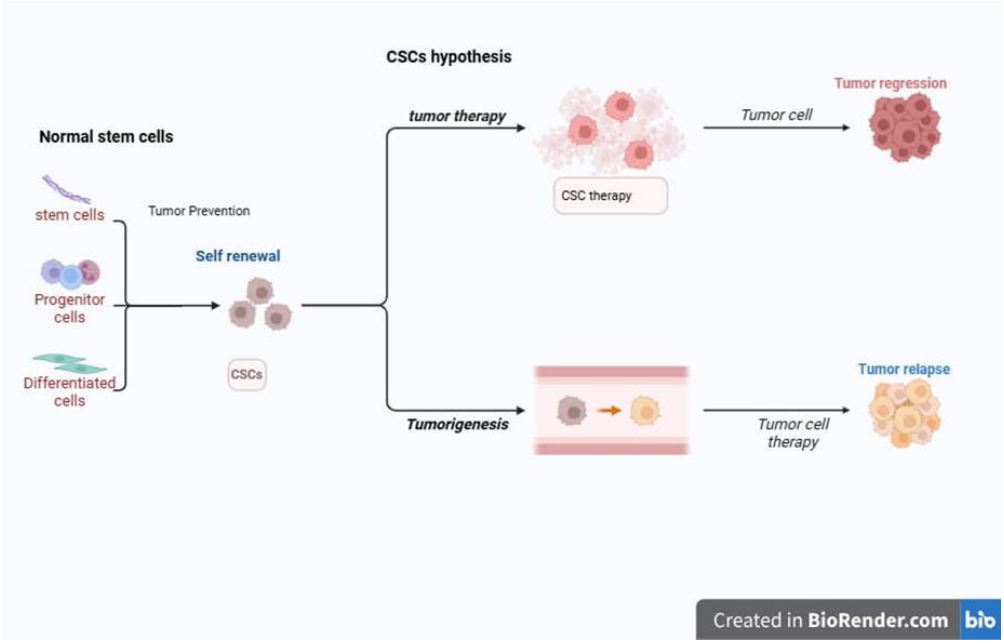
Molecular Mechanisms Underlying Plasticity of CSCs

CSCs were considered immobile body initially, at hold position at the top of the tumor cell hierarchy. It is now broadly ackn owledged that cancer stem cells become mobile and have elastic changes influences by their adjacent niche, a concept known as dynamic stemness model. Epigenomic shift triggered by some elements such as chronic inflammation, oxidative stress, hypoxic stimulus increases the

plasticity of conversion between the CSCs and non-CSCs. The Twofold aspect make CSCs help to adopt their niche, but their plasticity also complicate their clinical detection in vivo(Islam et al., 2015; Csermely et al., 2015; Harris & Best, 1988; Roesch et al., 2013).A fleeting decrease in the diversity of cancer caused by the treatment has been observed to reflect the enhancement of CSCs. This amplification occurs not only through the preference of therapy-resistant CSCs nut also through the decrease in the CSCs properties to CSCs. For example, sustained treatment with vemurafenib,a therapeutic agent that is used to target the V600E mutation in BRAF protein kinase. This protein is extremely oncogenic in the slow-cycling melanoma cells. Generally, CSCs are dormant and slow-cycling in the unfavorable conditions. As a result, melanoma CSCs when exposed to the vemurafenib turns less dependent on the oncogenic BRAF(V600E)-mediated signals helps in adaptive resistance in tumors to treatment.Acquired resistance to the anticancer therapies is believed to arise between signaling pathways and reversible epigenomic changes. For the effective treatment or elimination of CSCs, combined therapies involving two or three molecularly targeted drugs are used (Roesch et al., 2013)

Malignant Tumor Stem Cell Therapy

The cancer stem cell (CSC) hypothesis of tumor growth and progression states that a subset of tumor cells can self-renew and generate differentiated progeny, just like cells in healthy adult tissues. As in other tissues, stem cells, which comprise a small percentage of the entire organ, are the only cells that have the potential to persistently support tumor growth. Even though they make up the majority of the tumor's cells and are aggressively multiplying, the remaining cells are also differentiating and will eventually perish (Ailles and Weissman et al., 2007). Solid tumors make up the majority of malignancies, while epithelial cancers, which develop in organs such as the breastbone, pulmonary, the gastrointestinal tract, prostate tissue, and the ovaries, account for almost 80% of all cancers. Although they are less prevalent, other tumor types with extremely high fatality rates include pancreatic ductal adenocarcinoma and glioblastoma multiforme. Histology and the expression of certain markers are typically used to clinically evaluate tumors at the gross level. This has been used in conjunction with gene expression analysis to define different tumor subtypes (Hermann et al., 2010). Figure 2 presents diagrammatic representation of cancer stem cells (CSCs) and stem cells. Normal stem cell differentiation and proliferation are seen in the left panel. The right panel discusses the relationship between CSCs and carcinogenesis as well as how they may affect cancer treatment.



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Solid tumors represent a significant therapeutic barrier and a significant cancer burden. Many of these tumors demonstrate dormant behavior and treatment refractoriness, which can be explained by the appealing biological mechanism offered by the cancer stem cell (CSC) theory. There is mounting evidence that a specific subset of CSCs sustains and organizes a variety of solid tumors in a hierarchical manner. Although other forms of heterogeneity also appear to be relevant, mice models of epithelial carcinogenesis have lately provided direct evidence for the CSC theory. Although preliminary studies suggest that targeted targeting may be achievable, the clinical relevance of CSCs is still a basic problem (Visvader and Lindeman et al., 2008).

Therapeutics of Cancer Stem Cells

Origin of Breast CSCs

For many years, there has been debate in the profession over the ultimate origin of BCSCs. Whether BCSCs originate from multipotent mammary stem cells (MaSC), are a distinct progenitor population, dedifferentiate non-stem cells, or a combination of these is still unknown. The most commonly held belief is that progenitor cells and MaSCs give rise to BCSCs (Crabtree et al., 2018). Breast cancer is a disease that varies in histology, molecular makeup, and epidemiology. Based on gene expression studies, there are six molecular subtypes: basal-like, claudin-low, luminal A and B, normal breast-like, and HER2/ERBB2 over-expressing. Different transformation targets have been proposed as the cause of the molecular heterogeneity among breast tumors. The various epithelial populations in pre-neoplastic and normal tissue from

bearers of the BRCA1 mutation were investigated by Lim and associates (Mcdermott et al., 2010).

Breast Cancer stem cells Markers

Breast CSCs (BCSC) are among the best defined CSCs because they were the first to be prospectively shown in human solid cancers. such CSCs in other tumor settings, BCSCs have been enriched using a variety of phenotypic markers (such CD44+CD24−/lowLin−) and techniques (like the side population, ALDEFLUOR assay, and mammosphere), indicating that they are also diverse (Velasco-Velazquez et al., 2012). RPL39 and MLF2, two genes whose silencing in patient-derived tumor xenografts may lead to lower tumor volume and lung metastasis along with a corresponding decline in the expression of CSC markers, were among the 477-gene tumorigenic signature generated from patient BCSCs. Remarkably, half of breast cancer lung metastases had mutations in RPL39 and MLF2, according to RNA-Seq research. The ability of BCSCs to proliferate, invade, and self-renew was improved by the overexpression of the mutant genes. According to these findings, RPL39 and MLF2 are new "tumor-initiating" genes that affect lung metastasis and target BCSCs. The differences between BCSCs and the cell-of-origin of breast cancer have been hotly debated. It's interesting to note that while the BCSC was first described as having the CD44+CD24−/lowLin− phenotype, the CD24+/high and CD24−/low cells in certain patient tumors have different genetic changes, indicating that they came from different sources (Yang et al., 2014). Figure 3 shows signaling mechanisms controlling the activity of stem cells for breast cancer.

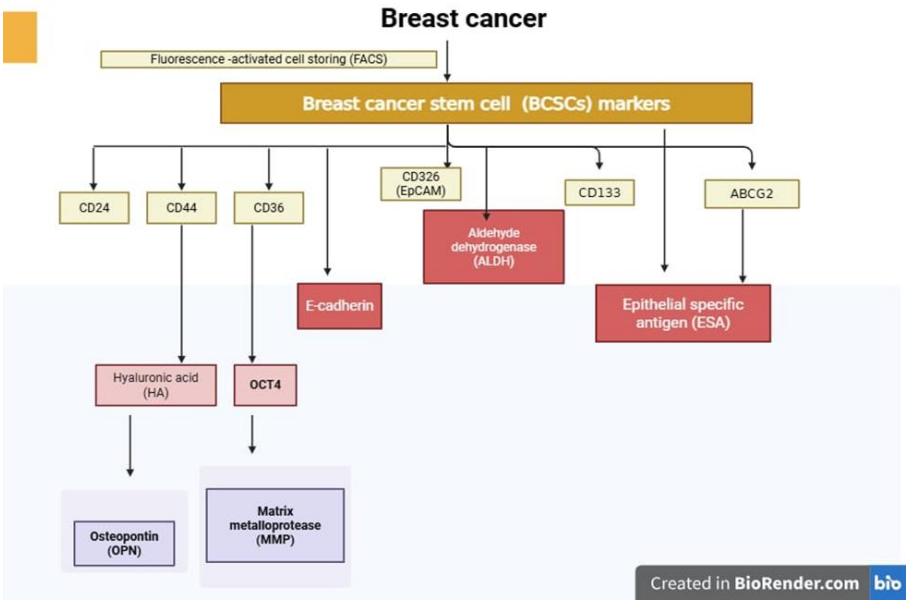

Fig. 3: Signaling mechanisms controlling the activity of stem cells for breast cancer (Image generated from biorender)

Signaling Pathways of Breast CSCs

During or after therapy, treatment resistance and a rise in BCSCs have been linked to the Notch, Hedgehog, and Wnt pathways. These mechanisms are essential for both adult tissue homeostasis and embryonic development (Bozorgi et al., 2015).

Wnt Pathway

Chemo resistance, radio resistance, migration, proliferation, and phenotypic shape of BCSCs are all strongly impacted by the Wnt pathway. The Wnt/β-catenin/TCF4 pathway increases miR-125b expression and chemoresistance in cancerous cells via using the Snail protein. In BCSCs, snail increases ALDH activity and CD44 marker expression. Prominent BCSC markers and novel Wnt targets are LRG5 and the protein C receptor (ProCr). MMP3 has been shown to help maintain BCSCs by targeting Wnt signaling. The Wnt/β-catenin pathway is positively targeted by a type VI intermediate filament protein called nestin, which increases BCSCs' capacity for metastasis (Song et al., 2021). According to (Farzaneh et al. 2021), PKF118-310 (PKF), a small molecule inhibitor of Wnt/β-catenin signaling, and Pyrvinium pamoate (PP), an anti-helminthic drug and a suppressor of the WNT pathway, target BCSCs in a HER2-overexpressing mouse model. These medications inhibit the growth of BCSCs and the expression of the genes OCT4, SOX2, and NANOG.

Hedgehog Pathway

Hedgehog signaling interacts using the Smoothened (SMO) protein to affect carcinoma and BCSC stemness. In order to help initiate BCSCs, a VEGF receptor known as neuropilin-2 (NRP2) stimulates the synthesis of α6β1 integrins and glioma-associated oncogene-1 (GLI-1). According to (Piers et al.,2016), GLI-1 promotes angiogenesis, which accelerates the progression of BCSC. α6β1 integrins have been shown to mediate BCSC self-renewal ability and trigger focal adhesion kinase (FAK) activation. Thus, concentrating on the VEGF/NRP2, α6β1, GLI1, and FAK signaling pathways may be an attractive therapeutic strategy for BC. An isoflavone found in soy products called genistein has been demonstrated to inhibit hedgehog downstream signaling, which hinders BCSC development and survival. According to (Feng et al., 2018). an aqueous extract of Trametes robiniophila Murr (Huaier) can inhibit hedgehog downstream signaling, hence reducing BCSC formation, proliferation, and self-renewal.

Mesenchymal-like traits, BCSC invasion, and treatment resistance can all be sustained via the Notch pathway through JAG-1 and NOTCH-4. A factor in the development of BC is NOTCH4, which targets GAS1 and SLUG [104]. The cytoplasmic Notch intracellular domain (NICD) in healthy cells is blocked by the NUMB protein, which also suppresses the Notch pathway (Wang et al., 2022). There have been findings that miR-146a causes BCSCs to form, suppresses NUMB function, and starts the Notch pathway. Therefore, downregulating the expression of miR-146a and miR-146b may impair BCSCs' capacity for self-renewal. MAP 17 (PDZKIP1) is a small cargo protein that promotes the Notch pathway,

suppresses NUMB activity, and helps maintain BCSCs.

Origin of Prostate CSCs

One widely held belief about prostate cancer genesis is that an AR-expressing cell from the luminal compartment has a longer lifespan and can move and initiate new growth in metastatic sites. A thorough examination of the genetic alterations found in the few accessible prostate cancer cell lines lends support to this viewpoint. For example, apoptotic suppressors such as Bcl2 are frequently overexpressed; telomerase activation46 enhances life expectancy; and tumor-suppressor gene activity (such as phosphate and tensin homolog-10) is diminished (Lang et al., 2009).

Therapy resistance in Prostate CSCs

CSCs and amplifying cells' gene expression patterns can provide some insight into the processes underlying treatment resistance. Similar to the highly advanced cells that were treated in the primary ailment, residual illness in other cellular systems is typically rudimentary in nature. The low residual amount of prostate cancer is easily explained by the AR-negative, basal nature of CSCs following castration treatments (Table 1) (Maitland et al., 2009).

Table 1: Important signaling pathways that play a role in the spread and metastasis of breast cancer stem cells (BCSCs).

Therapy	Primary Resistance	Secondary Resistance	References
Androgenic Therapy	CSCs AR negative	Genomic instability	(Ling et al,. 2018).
Radiotherapy	CSCs divide slowly	Expression of known radio resistance gene elevated in CSCs	(Olivares et al., 2020).
Chemotherapy	CSCs divide slowly	Expression of resistance to medication mutations, particularly ABC carriers, in stem cells	Lei et al., 2021).
Vaccination	Normally directed against the common isolated cell antigens, which are not present in CSCs.	Genomic Instability	Gammaitoni et al., 2014).
Genome Therapy	CSCs not express in common differentiating cells	Genomic instability	Prieto and Haider, 2021).

Strategies to get Removal of Prostate Cancer

The hazards of concentrating on stemness have not yet been assessed, and therapeutic methods to eliminate or restore mutant stem cells are still in their early stages of development. According to (Collins et al.,2009), there was a signal that could differentiate between cancer and benign stem cells as well as TA cells when determining the phenotypic differences between normal and malignant prostate stem cells. First, assay techniques for creating cancer medications now rely on a small number of cell lines for most tumor types, requiring a vast quantity of cells to be available. Prostate cancer stem cell cultures are not lines, and because of their limited cell supply, they do not last long. According to (Skvortsova et al.,2018), long-term culture is likely to produce subclones and variations that are selected by the culture environment due to their alleged natural DNA instability. Second, because the stem-cell compartment does not need rapid multiplication, the tests necessary to eradicate the CSCs cannot be evaluated by a slowing in growth rate or metabolism. If the stem cells were moved from the stem to the amplifying compartment, they would grow faster and be more susceptible to conventional mortality. (SLvortsova et al., 2018) Inducing differentiation from the AR-negative stem and TA compartments would also make the stem cells susceptible to various antiandrogen therapies.

Third, it is possible that the CSCs possess innate resistance mechanisms. Normal stem cells must possess the highly evolved ability to preserve stem-cell integrity in tissues, and there is no reason to believe that CSCs will not have done so. The most effective treatments will ultimately target all of the prostate's cellular compartments, revealing the stem-cell compartment once the 99% of cells that exhibit the AR-positive luminal phenotype have been destroyed (Tang and Dubrovska et al., 2018). Finally, the most effective treatments will eventually target all of the prostate's cellular compartments, revealing the stem-cell compartment once the 99% of cells that exhibit the AR-positive luminal phenotype have been destroyed. According to Tang and Dubrovska et al. (2018), normal stem cells must have the highly evolved ability to preserve stem-cell integrity in tissues, and there is no reason to believe that CSCs will not have done so. Third, the CSCs may have innate resistance mechanisms.

Conclusion

Cancer stem cells are not a novel idea. Studies of normal tissue stem cells and research indicating that cells with stem-like characteristics can be separated from solid tumors based on the expression of particular surface markers have recently sparked a renewed interest in this subject. Although the existence and characteristics of normal tissue stem cells are fascinating, they only obliquely support the idea that solid tumors contain stem cells. Because so many people are affected, breast cancer has drawn the greatest attention of all the cancer kinds. The idea that cancer stem cells, a subpopulation with a high proliferative and metastatic potential and the ability to serve as a reservoir for tumorigenicity, are the cause of therapy failure and resistance is supported by the isolation of BCSCs from a solid tumor and a thorough understanding of cellular, molecular, and signaling pathway mechanisms.

With stem cells on one side and conventional treatments like chemotherapy, radiation, and surgery on the other, cancer treatment has entered an exciting new phase. Aside from their well-known function in immuno-reconstitution, stem cells have garnered a lot of interest, particularly in light of emerging gene technologies like the ability to incorporate genes into eukaryotic cells, which enables more targeted administration of anti-cancer drugs. Instead of being attributed to rapidly proliferating cells, the disease may now be regarded as a cancer stem

cell problem.

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