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From Resistance To Remission: Disrupting Cancer Stem Cells For Better Therapies

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Abstract: Cancer continues to be one of the biggest health challenges we face globally, with traditional treatments often falling short because of tumor recurrence and resistance to therapy. Recent studies have shed light on the vital role that cancer stem cells (CSCs) play in tumor growth, metastasis, and treatment resistance. This review takes a closer look at the molecular mechanisms that fuel cancer stem cell (CSC) function, shining a light on key signaling pathways such as Wnt, Notch, and Hedgehog. It also explores innovative therapeutic strategies, including targeted therapies, immunotherapy, and stem cell-based methods, all designed to eliminate CSCs while leaving healthy tissues unharmed. Both preclinical and clinical studies show that therapies targeting cancer stem cells (CSCs) can enhance treatment effectiveness and lead to better patient outcomes. However, there are still significant hurdles to overcome, such as the diversity of tumors and the challenge of identifying specific CSC markers. Moving forward, research should concentrate on refining these therapeutic approaches to improve the accuracy and longevity of CSC-targeted treatments. This review offers important insights into how these therapies could revolutionize cancer treatment and boost patient survival rates.

Keywords: Cancer stem cells (CSCs), Tumor microenvironment, Metastasis, Therapy resistance, Targeted therapy, Immunotherapy, Stem cell therapy, Wnt pathway, Notch signaling, Hedgehog signaling, Tumorigenesis, Cancer progression.

1. INTRODUCTION

Cancer is a disease caused by genetic and epigenetic changes which take place in the somatic cells. It is characterized by abnormal growth of cells called Tumor or Neoplasm and has the ability to metastasize to different parts of the body. It is one of the most fatal illness worldwide and can be influenced by genetic and environmental factors.

The distribution of new cases and death in different regions of the world for both sexes together and for males and females individually is presented in Figure 1. In the year 2022, there were around 20.0 million new cases globally (19.96 million including NMSC and 18.73 million excluding NMSC) for both the sexes together and the number of cancer deaths was 9.7 million (9.74 million including NMSC and 9.67 excluding NMSC). In 2022, 49.2% of cases which comprises almost half of all new cases and 56.1% which is more than half of all cancer deaths, was reported to occur in Asia, where 59.2% of the population of the world lives. Among males, the most frequently diagnosed cancer was prostate cancer followed by lung cancer in 118 and 33 countries respectively and lung cancer followed by prostate and liver cancer was the leading cause of cancer death in 2022. Whereas in

females, breast cancer and cervical cancer were the most commonly diagnosed cancer and also the leading cause of cancer death followed by lung cancer in the year 2022.

Treatment of cancer has been a very complicated process. While traditional methods of treatment such as radiotherapy, chemotheraphy and surgery have been in use, major developments are being made in stem cell therapy, targeted therapy, ablation therapy nanoparticles, natural antioxidants, radionics, chemodynamic therapy, sonodynamic therapy, and ferroptosis-based therapy recently. Over the past few decades, practitioners and researchers of cancer have slowly changed their interest from focusing on cancer cells to paying attention to both cancer and stem cells. The incorporation of the two fields, the cancer and the stem cells fields, would lead to the generation of new therapies for cancer.

Stem cells are clonogenic cells which have the potential for self-renewal and multi-lineage differentiation. They are units of biological organization and carry out the function of development and regeneration. However, these processes can be interrupted by gene mutations or under some situations, resulting in the malignant transformation of the stem cells. These cells with plasticity, then become more and more aggressive and extremely resilient to unfavourable conditions such as anticancer treatment. Whether stem cells or any other cells which acquire characteristics like stem cells become the driver of cancer progression, however, remains unknown.

2. OBJECTIVE

This review shines a light on the crucial role that cancer stem cells (CSCs) play in tumor development, their resistance to standard treatments, and the potential therapies aimed at these cells. The research delves into the specific molecular processes that fuel tumor growth driven by CSCs, focusing on important signaling pathways such as Wnt, Notch, and Hedgehog. Additionally, it looks at current treatment strategies, such as immunotherapy, targeted therapy, and stem cell-based approaches, to offer insights into more effective cancer treatments. By analyzing the latest advancements in CSC research, we aim to contribute to the creation of new therapeutic strategies that can improve patient outcomes and reduce the likelihood of tumor recurrence.

3. MATERIALS AND METHODS

36 articles have been analyzed for the literature review. Keywords such as Cancer stem cells (CSCs), Tumor microenvironment, Metastasis, Therapy resistance, Targeted therapy, Immunotherapy, Stem cell therapy, Wnt pathway, Notch signaling, Hedgehog signaling, Tumorigenesis, Cancer progression were used for the literature searches in databases such as Google Scholar and PubMed.

4. RESULTS

A comprehensive review of 36 studies showed that CSCs played a vital role in tumor initiation, metastasis, and therapy resistance. Evidence from experimental and clinical studies demonstrated that CSCs exhibit enhanced self-renewal and plasticity, allowing them to evade conventional chemotherapy and radiotherapy. Key signaling pathways such as Wnt, Notch, and Hedgehog have been identified as crucial in regulating CSC functions. Research utilizing small-molecule inhibitors and monoclonal antibodies aimed at these pathways has shown promising results in preclinical trials, resulting in reduced tumor growth and recurrence. Additionally, immunotherapy approaches, such as CAR-T cell therapy and dendritic cell vaccines, have shown promise in specifically targeting CSCs while sparing normal stem cells from harm. The use of nanotechnology in drug delivery has also enhanced the accuracy of therapies aimed at CSCs, helping to lower systemic toxicity. However, challenges persist in differentiating CSCs from normal stem cells and tackling tumor heterogeneity. Moving forward, research should aim to refine therapeutic combinations and boost the specificity of CSC-targeting strategies to improve treatment effectiveness and patient outcomes.

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5. DISCUSSION

5.1 Cancer Stem Cell Theory: Origin and Implications

Historical perspective and evolution of CSC theory:

Rudolf Virchow and his student Julius Cohnheim were among the first to discuss undifferentiated cells' role in cancer in 1877. The early theories such as Cohnheim's embryonic rest theory postulated, that tumor formation originates from dormant embryonic cells left unused during development. If these cells receive an adequate blood supply, they proliferate uncontrollably, leading to tumor growth. This theory was built on earlier observations by Johannes Müller and Virchow, who noted similarities between embryonic and tumor development.

Although the Embryonic rest theory emerged as an alternative to parasitic and chemical theories of cancer, its acceptance was undermined by a lack of clinical validation. In the year 1907 Max Askanazy introduced the concept of stem cells, he described them as embryonic remnants with delayed or enhanced maturation which brought a new perspective to cancer research.

Later, Theodor Boveri's **chromosomal theory of cancer** proposed that unusual chromosome distribution during cell division leads to uncontrolled proliferation. His argument suggested that chromosomal abnormalities were responsible for immature traits of cancer cells rather than embryonic remnants. This perspective was prevalent for many years and portrayed cancer cells as differentiated rather than stem-like.

However modern cancer stem cell research was shaped by studies on teratocarcinomas conducted in the 1960s and 1970s which rekindled the interest in the role of stem cells.

Definition and characteristics of CSCs

According to Cancer stem cell theory, certain cells have unique inherent properties that allow them to withstand radiochemotherapy and enhance their metastatic potential. The rapid progression of Cancer stem cells has been associated with a rise in the risk of tumor relapse, metastasis, and poorer clinical outcome. There is a need to study intratumoral heterogeneity using advanced techniques like CRISPR-Cas9 screens to identify new targeted therapies. This allows us to explore the discovery and characteristics of CSC populations across major cancer types, innovative methods for studying therapy-resistant tumor cells, and the latest advancements in CSC-targeted treatments.

Studies suggest that cancer stem cells (CSCs) are present in nearly all types of human cancers that are characterized by their self-renewal ability and resistance to conventional therapies. CSCs persist mainly within tumors and enter standard antimitotic and molecularly targeted treatments unlike actively proliferating and differentiated cancer cells. Their clinical significance lies in their role in therapy resistance, tumor relapse, and metastasis. While surgery, chemotherapy, and radiotherapy have long been the mainstays of cancer treatment, immunotherapy is becoming more popular, particularly in advanced-stage cases. However, effectively targeting CSCs continues to be difficult due to the absence of unique molecular markers. Recent immunological studies focus on targeting CSCs based on their antigen expression profile, though potential off-target effects on immune cells limit their effectiveness. Given the ability of CSCs to influence immunotherapy response, a combination therapy approach—targeting CSCs alongside the tumor microenvironment (TME) while integrating conventional treatments—could provide a more effective strategy for eliminating cancer cells.

CSC Identification and Markers

Cancer stem cell (CSC) biomarkers can be identified based on their abnormal signaling and metabolic pathways and can be divided into cell surface markers and intracellular markers. Surface markers, are mainly transporters and signaling receptors and are highly significant as they enable targeted delivery of diagnostic and therapeutic agents to CSCs. For instance, melanoma CSCs are frequently linked to ABCB5, a transporter belonging to the ATP-binding cassette sub-family, whereas lung, pancreatic, liver, breast, and ovarian cancer CSCs are biomarked by ABCG2. While certain markers, such as ABCG2, are more specific, others are shared by several cancer kinds. While CD34 is a crucial indicator

for leukemia CSCs rather than solid tumors, CD133, a glycoprotein associated with cholesterol binding, is present in breast, liver, lung, and ovarian cancer CSCs.

CSCs have also been identified using cell surface markers, such as CD44, an adhesion receptor that is well-recognized in a variety of adult and stem-like cells. It is frequently employed as a biomarker for glioblastoma CSCs, breast cancer, and colon cancer.

Cell surface markers have also been instrumental in identifying CSCs, with **CD44**, an adhesion receptor, well known across various stem-like and adult cells. It is commonly used as a **biomarker for breast cancer, colon cancer, and glioblastoma CSCs**. These markers have facilitated the development of **antibody- and aptamer-based technologies** for CSC detection and targeted therapies in preclinical studies. Therapeutic agents, such as **small molecules, proteins, nucleic acids, and nanoparticles**, can be modified with specific antibodies or ligands to improve CSC targeting. However, a major limitation is that these markers **lack specificity** and are also present, though in lower amounts, in non-stem cancer and healthy cells.

5.2 Signaling Pathways Shared by Stem Cells and Cancer Cells

Resistance to anticancer therapies is the main challenge faced during cancer treatment as it reduces the effectiveness of chemotherapy, radiotherapy, molecularly targeted therapy, and immunotherapy.

Resistance is classified into two types intrinsic and acquired. Intrinsic resistance arises from pre-existing genetic or phenotypic variations within a subpopulation of cancer cells, enabling them to counteract therapy whereas acquired resistance develops during treatment due to therapy-induced selection of resistant cellular states or through genetic and phenotypic adaptations a key factor in both types of resistance is the role of developmental signaling pathways.

Among these pathways, Notch, Hedgehog, and Wnt are critical as they regulate cellular growth, differentiation, and migration.

Notch Signaling in Cancer Resistance:

Notch signaling pathway is involved in various developmental processes such as germ layer formation and cellular differentiation in adults this pathway monitors cell proliferation, apoptosis, migration, angiogenesis, and epithelial-mesenchymal transition, the pathway consists of four Notch receptors (Notch 1–4) and five ligands (Jagged-1, -2, and Delta-like-1, -3, -4), all of which are type I transmembrane proteins.

Cell to Cell interactions are initiated by Notch signaling pathway whereas proteolytic cleavages are activated by ligand signaling. The first cleavage{S2} is caused by ADAM10/ADAM17 extracellularly. Whereas γ-secretase initiates the second cleavage{s3} in the transmembrane domain. This phenomenon results in the release of Notch intracellular domain (ICN), which translocate to the nucleus and interacts with RBPJ (CBF1/Suppressor of Hairless/Lag-1), converting a transcriptional repressor complex into an activator complex.The activation of Notch signaling is associated with various cancers and contributes to drug resistance by promoting cancer stem cell survival, tumor progression, and therapy evasion. Due to its role in treatment resistance, Notch signaling is a promising target for novel therapeutic strategies.

Hedgehog Signaling and Cancer Resistance:

The Hedgehog (Hh) signaling pathway plays a crucial role in embryonic development and adult tissue maintenance, by regulating processes like repair, differentiation, and stem cell renewal. It mainly includes three ligands (Shh, IHH, DHH), the PTCH receptor, SMO, SUFU, and GLI transcription factors. Normally, PTCH inhibits SMO, but ligand binding lifts this suppression and activates GLI-mediated gene transcription.

The atypical activation of Hedgehog signaling has been associated with various malignancies, which include blood cancers and solid tumors, where it promotes tumor growth, progression, and resistance to therapy. In hematological cancers like chronic myeloid leukemia (CML) and acute myeloid leukemia (AML), Hedgehog signaling maintains

leukemic stem cells, allowing the disease to sustain. Inhibition of this pathway has been shown to reduce leukemia development and enhance survival rates in experimental models. Additionally, in AML, combining Hedgehog inhibitors with 5-azacytidine has demonstrated enhancing effects by reducing leukemia-initiating stem cells.

In solid tumors, particularly basal cell carcinoma (BCC), mutations in PTCH1 (found in 70–90% of cases) and SMO (in 10–20% of cases) drive unchecked Hedgehog signaling, contributing to tumor formation and resistance to treatment. Due to its role in therapy resistance, targeting Hedgehog signaling remains a promising strategy for improving cancer treatment outcomes.

Wnt Signaling and Cancer Resistance:

The Wnt signaling pathway plays a very important role in the regulation of development, stem cell proliferation, and tissue homeostasis. Disruption of this pathway can lead to diseases such as birth defects and cancers. The canonical (β-catenin-dependent) and non-canonical (β-catenin-independent) pathways are activated by Wnt ligands binding to Frizzled (Fz) receptors. Canonical signaling stabilizes β-catenin, allowing it to enter the nucleus and regulate gene expression. In contrast, the inactivated pathway leads to β-catenin degradation via the GSK-3/APC/Axin complex.

Wnt signaling plays a crucial role in carcinogenesis, first identified in colorectal cancer through APC mutations and β-catenin stabilization. Further research has linked aberrant Wnt activation to breast, pancreatic, lung, and prostate cancers, melanoma, and hematological malignancies (AML, CML, B-ALL, CLL, and Multiple Myeloma). Understanding Wnt dysregulation offers potential targets for cancer therapy.

5.3 Therapeutic Implications of Targeting Cancer Stem Cells

Cancer stem cells (CSCs) represent a subpopulation of cancer cells that have the potential to self-renew, differentiate, and subsequently propagate tumor growth and progression. CSCs are believed to be responsible for the relapses and metastasis observed in cancers. Targeting CSCs seems to be a promising option for therapy, albeit with several challenges due to their distinct biological features and characteristics.

Origin of Cancer Stem Cells

There are two models of origin for CSCs. The first model suggests that CSCs arise from normal stem cells subjected to genetic mutation. The second model proposes that lineage-restricted progenitor cells could also give rise to CSCs with properties of self-renewal. In certain studies, it was suggested that the differentiation capacity of drug resistance-leukemia stem cells may lie somewhere in between stem and differentiated progenitor cells.

Therapeutic Strategies Targeting CSCs:

Several therapeutic strategies have been developed to target cancer stem cells:

- Disruption of central regulating signaling pathways: For example, those River targets Sonic hedgehog (Shh)/Patched (Ptch)/Smoothened (Smo), Notch/Delta-like ligand (DLL), CXC chemokine receptor 1-2/CXCL8/FAK, and Wnt pathways.
- Inhibition of specific markers: Some examples include CD44, CD133, and other cell-surface markers.
- Inhibition of ABC transporters: Three generations of drugs have been developed to inhibit ABC transporters overcoming chemoresistance in CSCs.
- Manipulation of miRNA expression: Non-coding RNAs target regulating CSC properties and functions.
- Differentiation and apoptosis agents: Agents such as retinoic acid and its analogs to induce differentiation in CSCs.

Cancer Vaccines and Immunotherapy:

Cancer vaccines and immunotherapy represent promising strategies to target CSCs. These include:

- Cancer vaccines: Developed to train the immune system to recognize and attack CSCs.
- Dendritic cell vaccines: Dendritic cells stimulate antigen-presenting cells and develop DC-based vaccines against CSCs.
- Peptide vaccines: Designed to target specific peptides associated with CSCs.
- Adoptive cell therapy (ACT): Antigens derived from CSCs are used to stimulate antigen-presenting dendritic cells and develop DC-based vaccines targeting CSCs.

Nanoparticle-Based Drug Delivery Systems:

Nanoparticle-based drug delivery systems are being developed for targeting cancer stem cells. They include:

- Nanoparticles (NPs) for the drug delivery of therapeutic agents directly toward CSCs, enhancing the solubility, bioavailability, and efficacy of the drugs.
- Liposomes: Non-toxic and biocompatible vesicles used to deliver drugs to cancer stem cells.
- Carbon nanotubes (CNTs) for drug and gene delivery to cancer stem cells.
- Gold nanoparticles (GNPs) against photothermal therapy (PTT) for targeting cancer stem cells.
- Quantum dots (QDs) for targeted drug delivery to cancer stem cells

Targeted Therapies:

Targeted therapies are being developed to target specific markers on cancer stem cells. These so far include:

- Hyaluronic acid (HA) to target CD44, a common receptor on cancer stem cells.
- CD133-targeted nanocarriers to target CD133+ cancer stem cells in various cancers.
- EpCAM-targeted nanocarriers to target EpCAM+ cancer stem cells in various cancers.
- ALDH-targeted nanocarriers to target ALDH+ cancer stem cells in various cancers.

Photothermal Therapy (PTT):

PTT is a useful approach in targeting CSCs. Here, metal NPs convert light into heat to evoke a hyperthermal physiological response to target CSCs.

Magnetic Fluid Hyperthermia (MFH):

MFH is yet another way to target CSCs, exploiting the great thermal conversion efficiency of magnetic NPs under an alternating magnetic field to induce localized hyperthermia within a tumor.

Gamma-Secretase Inhibitors (GSIs):

GSIs act by inhibiting gamma-secretase enzyme activity, which is important in several cellular functions, including the cleavage of specific transmembrane proteins. GSIs have the ability to inhibit the Notch signaling pathway-an important player in cell differentiation, proliferation, and survival.

Isolation and Enrichment of CSCs:

Some methods adopted for isolating and enriching CSCs are as follows:

- Flow cytometric-based differential sorting: For isolating and enriching CSCs based on specific cell surface markers.
- Hoechst 33342 dye exclusion uses: Isolation and enrichment of CSCs based on the exclusion of Hoechst 33342 dye.
- ALDH Enzymatic activities: For isolating and enriching CSCs based on ALDH enzymatic activities.
- Colony-forming assay: Used to isolate and enrich CSCs according to their ability to form colonies.
- Cancer sphere formation: Used to isolate and enrich CSCs based on their ability to form cancer spheres.
- Cancer induction in nude mice models: Used to isolate and enrich CSCs on their ability to induce cancer in nude mice models.

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Therapeutic Strategies Targeting CSCs and their Microenvironments

- CSC Targeting Strategies: Disrupting central regulating signaling pathways, targeting specific markers, inhibiting ABC transporters, manipulating miRNA expression, and inducing differentiation and apoptosis.
- Targeting Classic Markers of CSCs: CD13, CD44, CD133, and EpCAM.
- Targeting the Niche of CSCs: Hypoxic microenvironment, acidic microenvironment, tumor-associated macrophages (TAMs) and cancer-associated fibroblasts (CAFs), chemokines, and cytokines.
- Targeting Classic Pathways of CSCs: WNT pathway, Sonic hedgehog pathway, Notch pathway, and JAK/STAT pathway.

5.4 Challenges in Differentiating Normal Stem Cells from Cancer Stem Cells and Future Directions: Stem Cell Research in Cancer Therapy and Prevention

Biomarkers and Cancer Stem Cells (CSCs)

Isolation and identification of cancer stem cells (CSCs) from non-CSCs have biological and clinical implications. Biomarkers, derived either from DNA, RNA, or proteins, detected within the tumor or in the blood, are critical for diagnosis, prognosis, and the construction of therapy.
• Biomarkers help identify, monitor, and target cancer.
• A CSC-targeted biomarker may delineate tumor heterogeneity and improve prognosis and therapy design.
• The difference between stem cell theory vs. genetic theory of cancer can allow for monitoring cancer evolution and maximizing treatment efficacy.

Differences Between Normal Stem Cells and Cancer Stem Cells (CSCs)

1. Self-Renewal & Differentiation
   - Normal stem cells and CSCs both have self-renewal capacity and can give rise to progeny cells.
   - Normal stem cells maintain tissue homeostasis through regulated differentiation.
   - CSCs play a role in uncontrolled tumor proliferation and metastasis.

2. Tumorigenicity
   - Normal stem cells do not form tumors upon transplantation.
   - CSCs are tumorigenic, i.e., they possess the capacity to initiate and sustain tumor formation.
3. Resistance to drugs & Survival Mechanisms
   - Normal stem cells employ detoxification and antioxidation processes for protection and durability.
   - CSCs exploit these very same processes (e.g., ABC transporters, anti-apoptotic processes, GST overexpression) to become resistant to chemotherapy and consequently are resistant to a various treatments and lead to tumor recurrence.
   - The TRADD/NFkB survival pathway and PI3K/AKT signaling pathway enable normal stem cells and CSCs to survive against stress, but in CSCs they increase resistance to drugs.
   - Elevated GST levels in CSCs facilitate resistance via mechanisms that involve MAP kinase and NFkB.
4. Genomic Stability
   - Normal stem cells possess rigorous genomic integrity.
   - CSCs acquire genetic instability, which allows for rapid tumor evolution and resistance to treatment.
5. Microenvironment Interaction
   - Normal stem cells respond to physiological signals for restoration and healing.
   - CSCs alter over the tumor microenvironment to support their growth, evade immune rejection, and resist therapy.
6. Interconversion Potential
   - Normal stem cells display a stable differentiation hierarchy.

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- CSCs can alternate between tumorigenic and non-tumorigenic states, indicating that tumorigenicity may be reversible and context-dependent.
- This interconverting process makes CSC-targeted therapies challenging, since cells are able to develop resistance to therapies by changing states.

What Makes a Cancer Stem Cell Unique?

Tumorigenic Characteristics

Cancer stem cells (CSCs) are a minority of cells within a tumor and are also known as tumor-initiating cells or tumorigenic cells. While they share many characteristics with normal stem cells, they differ in their ability to:

- Form tumors when injected into animals, unlike normal stem cells.
- Be chemoresistant, causing the tumor to recur.
- Drive metastasis, spreading cancer to other areas.

  Surface Markers and Identification of CSCs:

  Both CSCs and regular stem cells share common surface markers, and it becomes hard to distinguish between them. The most common method used to separate CSCs is fluorescence-activated cell sorting (FACS) with specific markers:
- CD133, CD24, and CD44 are commonly associated with CSCs.
- The CD34+CD38− markers are present in leukemic stem cells, differentiating them from normal hematopoietic stem cells.
- Emerin-positive (ESA+) CD44+CD24−/(low) phenotypes are found in breast cancer stem cells.

Functional Assays for CSC Identification:

Because surface markers alone may not be sufficient, CSCs are also identified by functional assays:

- Sphere-forming assays: CSCs can form spheres or colonies in serum-free or soft agar.
- Transplantation assays: Tumor cells are transplanted into immunocompromised mice to assess their ability to regenerate tumors over multiple generations.

These methods help confirm CSC identity and provide insight into their role in tumor propagation and resistance to treatment.

Models of Cancer propagation:

There are several models of cancer spread, including the cancer stem cell model, the clonal evolution model, and the interconversion model. The CSC model suggests that only a subset of cancer cells have tumorigenic potential, while the clonal evolution model suggests that genetic instability is the cause of generating heterogeneous tumor populations of cells having a variety of tumorigenicities. The interconversion model introduces the notion of bidirectional plasticity by which tumorigenic and non-tumorigenic states are switched by cancer cells in response to microenvironmental cues.

Stem Cell-Based Cancer Therapies:

Cancer treatment is constantly rising , and among the most significant challenges faced by cancer therapy is the presence of cancer stem cells that have a tendency to survive traditional therapies resulting in tumor recurrence making it increasingly difficult to eliminate the disease.

In response to this, researchers are developing treatments against CSCs alone, to inhibit pathways leading to CSC survival and self-renewal, thus reducing the risk of recurrence.

Immunotherapy is also a promising approach, where engineered stem cells like CAR-T and TCR-engineered cells allow the immune system to identify and destroy cancer more effectively. Additionally, regenerative medicine with induced pluripotent stem cells (iPSCs) is under exploration in order to regenerate tissues destroyed by chemotherapy and radiation, enhancing recovery and minimizing treatment-associated complications. Scientists are also using stem cells to deliver drugs, nanoparticles, and even viruses directly to tumors and target the disease, reducing toxic side effects. All these advances offer new hope for cancer, looking for better outcomes with fewer problems.

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Stem Cell Sources:

Stem cells form a unique class of cells that share their unlimited capacity for self-renewal, the potential to produce single cell-derived clonal populations, and the ability to differentiate into cell types. Resident pools of stem cells' self-renewal is crucial in tissue regeneration and homeostasis. Stem cells are broadly divided into Embryonic Stem Cells (ESCs) and Somatic Stem Cells (SSCs) (otherwise known as adult stem cells).

SSCs are generally multipotent and differentiate into lineage-specific cells, including Neural Stem Cells (NSCs), Mesenchymal Stem Cells (MSCs), Hematopoietic Stem Cells (HSCs), Endothelial Progenitor Cells (EPCs), and Cancer Stem Cells (CSCs), which can contribute to tumorigenesis.

- Embryonic Stem Cells ESCs are pluripotent but can differentiate only into all somatic cell types except placental cells. Their application in therapy and research, however, is limited by ethics. Induced Pluripotent Stem Cells (iPSCs) are reprogrammed from the adult somatic cells, precluding ethical considerations and offering clinical utility similar to ESCs.
- Neural Stem Cells (NSCs) contain specific neural markers and are able to differentiate into neurons, astrocytes, and oligodendrocytes. They have been used for the treatment of numerous cancers like lung, breast, prostate, and brain cancers.
- Mesenchymal Stem Cells (MSCs) are of bone marrow origin and have the ability to differentiate into mesodermal cells including cartilage, bone, and adipose tissue. Due to their ease of isolation and growth, they are being utilized very widely in cancer therapy.
- Hematopoietic Stem Cells (HSCs), predominantly located in bone marrow, give rise to differentiated mature blood cells. Clinically, they have been employed for over four decades in the treatments of transplant.
- Endothelial Progenitor Cells (EPCs) are engaged in vascular regeneration and hold cancer therapeutic potential. Existing studies are focused on their participation in disease aetiology and treatment.

Stem Cell Modifications for Cancer Therapy:

Stem cells, including neural stem cells (NSCs) and mesenchymal stem cells (MSCs), may be modified by a number of mechanisms for a variety of cancer treatments. Principal modifications consist of enzyme/prodrug systems, drug delivery using nanoparticles, oncolytic virus delivery, and engineered secreted factors in tumor sites.

1. Enzyme/Prodrug Therapy
   NSCs and MSCs may be engineered to produce enzymes catalyzing conversion of non-toxic prodrugs to toxic drugs. The method allows for temporal, spatial, and quantitative control over the release of a drug, which minimizes systemic toxicity. The enzyme cytosine deaminase (CD) metabolizes 5-fluorocytosine (5-FC) to 5-fluorouracil, a very toxic drug. It was demonstrated by experiments that CD-transduced NSCs and MSCs effectively inhibited glioblastoma (GBM) development when treated with 5-FC.
   HSV-TK phosphorylates ganciclovir (GCV) into a cytotoxic metabolite that incorporates into DNA of actively proliferating tumor cells and induces apoptosis.
   HB1.F3.CD cells, an ordinary cytotoxic treatment, show CD expression to enhance the anti-tumor activity.
2. Secreted Therapeutic Agents
   Stem cells may be designed to secrete continuously antitumor agents, preventing short drug half-life and high systemic toxicity.
   TRAIL is a highly utilized pro-apoptotic drug inducing tumor apoptosis. Controlled delivery of the same within synthetic extracellular matrix (sECM) leads to controlled release hindering re-growth of GBM and improved survival in animal models.
   IFN-β-producing MSCs suppress tumor cell growth through in-activation of the Stat3 signaling pathway, suppression of tumor cell proliferation, angiogenesis, and metastasis.
   3. Viral Therapy
   Oncolytic viruses (OVs) selectively replicate in tumor cells, expanding targeted therapy with little recognition by the

immune system.
NSC-delivered oncolytic viruses showed enhanced antitumor activities against GBMs, especially following radiotherapy and temozolomide treatment.
Viral delivery mediated by MSCs is promising for cancer therapy such as hepatocellular carcinoma, where measles virus-infected MSCs homed to the tumor and strongly inhibited growth.
Oncolytic herpes simplex virus (oHSV) with TRAIL-expressing MSCs triggered apoptosis and enhanced survival in GBM-bearing mice.
4. Nanoparticle-Based Drug Delivery
Nanoparticles (NPs) enable targeted drug delivery, protecting therapeutic agents from degradation and immune surveillance.
Porous silica nanorattle-loaded doxorubicin in MSC membranes exhibited enhanced drug delivery and caused more effective tumor apoptosis than free drug treatment.
Micro-metastatic lesion-targeting and effective avoidance of unproductive drug release in solid tumors are facilitated through NP delivery systems based on MSC.

Other applications of stem cells in cancer therapy:

1. Regenerative Medicine
Stem cells can self-renew and differentiate, hence their relevance in the restoration of human tissues after chemotherapy. Hematopoietic stem cell (HSC) transplantation has been applied routinely to facilitate permanent hematological reconstruction after high-dose radiotherapy or chemotherapy. This therapy is designed to:
• Reconstitute bone marrow in failure states (e.g., aplastic anemia).
• Cure genetic blood cell disorders by supplying stem cells that differentiate into specific forms of blood cells.
• Enable hematopoiesis—successful engraftment of one HSC can normalize hematopoiesis in recipients.
Healthy induced pluripotent stem cells (iPSCs) derived from patient tissues can potentially be used for regenerating tumor- or treatment-damaged tissues. iPSCs have the potential to repair or replace damaged tissues following chemotherapy, radiotherapy, or surgery. Effective regenerative therapy, however, requires robust in vivo engraftment of iPSC-derived tissues. So far, only a few iPSC-derived cell types, such as hepatocytes, have been engrafted effectively in animal models.
2. Immunotherapy
Allogeneic HSC transplantation can induce an immune-mediated anti-tumor effect with the potential of curing specific hematological malignancies. HSCs transduced with CARs or TCRs recognizing tumor-associated antigens have also been shown to be hopeful in cancer immunotherapy.
Patient-derived iPSCs would potentially make immunotherapy more efficient. iPSCs derived from T lymphocytes can host pre-rearranged TCR genes, and they can be differentiated back to tumor antigen-specific functional T cells. Reprogrammed T cells could be administered to patients to enhance antitumor immunity. However, the safety of iPSCs derived from T cells needs to be more verified before they could be used.
3. Targeting Cancer Stem Cells (CSCs)
CSCs are multipotent, highly proliferative, and are responsible for tumor invasion and metastasis. CSC targeting is critical for improving therapeutic efficacy and preventing tumor recurrence .
Normal stem cells can be used to target CSCs in cancer therapy. Normal stem cell-CSC interactions can suppress:
• Tumor growth
• Angiogenesis
• Metastasis
• Inflammation and apoptosis
Bryukhovetskiy compared the potential of neural stem cells (NSCs) and HSCs for the treatment of glioblastoma. According to their findings, HSCs are more appropriate for the treatment of glioblastoma since they are less prone to

neoplastic transformation than NSCs. Engineered HSCs would also allow the development of targeted CSC apoptosis-inducing therapies.

4. Anticancer Drug Screening
   iPSCs also provide an advanced anticancer drug-screening platform. Cell types generated by differentiating patient cancer tissue-derived iPSCs are more representative of human tumors compared to current screening models, such as:
   • Cancer cell lines
   • Mouse xenograft models
   •Mouse tumors
   Besides, hepatotoxicity screening is a critical step in drug development. Many antitumor drugs fail in clinical trials due to toxicity concerns. Human iPSC-derived hepatocytes with diverse genetic backgrounds can be used to screen for hepatotoxicity, improving drug safety evaluation

Stem Cell Type:
While all stem cells share similar properties, their therapeutic effects can vary significantly.
Ahmed compared neural stem cells (NSCs) and mesenchymal stem cells (MSCs) as carriers for an oncolytic adenovirus in a glioma model. Both NSCs and MSCs supported intracellular adenoviral replication, but NSCs released significantly more virus than MSCs ($p < 0.001$). Intracranial administration of virus-loaded NSCs led to prolonged survival (median survival: NSCs: 68.5 days vs. MSCs: 44 days, $p < 0.002$). Despite similar migration potential, NSCs showed greater therapeutic effect in intracranial tumors. Stem cell carrier efficacy may be due to cellular origin similarities with malignant cells.
For cancer therapy, the selection of the type of stem cell depends on cell-specific characteristics and the goals of treatment. Autologous hematopoietic stem cell (HSC) transplantation is the norm for treating hematologic and non-hematologic malignancies and for hematopoietic rescue after high-dose chemotherapy. It is also best for treating congenital and acquired marrow failures to enable continual blood cell replenishment. Induced pluripotent stem cells (iPSCs), however, are highly suitable for testing the toxicities of candidate antitumor drugs.

Route of Transplantation:

The route of stem cell delivery plays a critical role in anti-tumor therapy. An appropriate method must consider:

- Target pathology
- Therapeutic objectives
- Patient risk-benefit profile

Delivery Methods:

Intracranial Injection

- In **murine models of GBM**, efficient **neural stem cell (NSC) delivery** is achieved via **contralateral injection** into the tumor site.However, this method is highly **invasive** and **not ideal for repeated operations**.

Intranasal Delivery

- NSCs delivered intranasally can efficiently migrate to tumor tissues.
- Enables repeated administration without additional surgeries.
- Avoids complications associated with intravascular delivery, such as:
  - Pulmonary embolism
  - Blood-brain barrier obstruction
  - Infarctions

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Enhancing Transplantation Efficiency:

Semisolid Substrates vs. Cell Suspensions

- Compared to cell suspension injections, semisolid substrates offer:
    - Mechanical support
    - Reduced metabolic stress
- Poor survival of NSC grafts can be addressed through biocompatible transplantation devices.

3D Extracellular Matrix-Based Substrates (3DECM)

- Hansen developed a 3DECM purified from engineered skin cultures, improving clinical transplantation efficiency.
- Benefits of 3DECM:
    - Enables in vitro expansion of embedded NSCs.
    - Retains uncommitted differentiation potential

Challenges to Stem Cell Therapy

1. Treatment Durability:

Tumors often relapse despite strong initial therapeutic effects. Like most chemotherapies, stem cell therapy using a single agent generally cannot completely eliminate tumors. To enhance treatment durability, an optimized drug combination should be rationally selected. Some combination treatments have been examined, including:

• IFN-β immunotherapy + chemotherapy with a prodrug/suicide gene system has shown synergistic therapeutic activity against human colorectal cancer.

• Irradiation of tumour cells was found to stimulate the secretion of factors that cause MSC invasion through basement membranes, facilitating the accumulation of MSCs in tumours.

• Stem cell-based oncolytic virotherapy + chemoradiotherapy minimizes residual disease volumes and sensitizes glioma cells to CRAd-S-pk7 (OV CRAd-Survivin-pk7) during radiotherapy.

• TMZ sensitization + MSC-TRAIL gene therapy enhances antitumor effects by modulating apoptotic machinery, as demonstrated in glioma cells.

•TRAIL + EGFR-targeting stem cell therapy enhanced treatment of tumors with overexpressed EGFR, which is a poor prognosis indicator.

2. Potential Tumorigenesis Concerns:

Normal stem cells and CSCs have significant characteristics in common:

- Self-renewal
- Differentiation
- Epithelial-to-mesenchymal transition capabilities

This similarity raises concerns that stem cell therapy may inadvertently increase cancer risk. A case in the literature exhibited tumor four years after fetal neural stem cell transplantation for ataxia-telangiectasia. Further studies are warranted to fully understand and minimize these risks.

However, it is uncertain if stem cells directly facilitate tumor growth or simply develop tumors themselves.

Karnoub demonstrated that:

• Bone marrow-derived MSCs, when mixed with weakly metastatic human breast carcinoma cells, increased their metastatic potential in subcutaneous xenografts.

• MSC-secreted chemokine CCL5 (stimulated by breast cancer cells) acted in a paracrine manner, enhancing cancer cell motility, invasion, and metastasis.

• This increase in metastatic capability was reversible and dependent on CCL5 signaling through the chemokine receptor CCR5.

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Thus, MSCs within the tumor microenvironment may facilitate metastasis by temporarily altering cancer cell phenotypes, emphasizing the need for further safety evaluations in stem cell therapies.

Future Strategies and Directions for Targeting CSC:

Target discovery is challenging due to their scarcity and difficult characterization. Even so, newer technologies in high-throughput sequencing, including single-cell RNA sequencing, offer the potential to fine-tune definitions of CSC and identify new therapy targets. In looking at cell populations within a tumor for trends in stemness-related expression patterns, scientists have the ability to construct detailed genomic and epigenomic profiles for CSCs that do not use burdensome tumor initiation assays for reference.

Tirosh employed single-cell RNA sequencing of the primary lesion in oligodendroglioma patients and identified three patterns of expression that coincided with oligodendrocyte markers, astrocytic markers, and an intermediate with stem-like cell-like appearance. This may assist in the identification of novel targets for drug therapy for CSCs in oligodendroglioma and other cancers. Barcode-tagging and tracking in vivo have also identified CD109+ metastatic CSCs in lung cancer.

Role of Bioinformatics and Artificial Intelligence:

The intersection of big data and AI is poised to drive CSC research. Machine-learning and deep-learning algorithms have already been applied effectively in cancer diagnosis, e.g., Esteva's convolutional neural networks in skin cancer. The explosion of multiomic data and bioinformatics tools offers a new window of opportunity for CSC-targeting methodologies, facilitating the streamlining of cancer treatment and research.

Despite these advances, there is a large translational divide between the clinic and laboratory. Although numerous CSC-targeting clinical trials are under way, they enroll only 4–5% of cancer patients. Hindrances are data-sharing limitations, organizational inefficiencies, restricted access to information, and poor coordination between bioinformaticians and cancer biologists. Abolishing these bottlenecks using harmonized collection and integration of data can maximize CSC-targeting strategies and ultimately lead to improved cancer treatments.

6. CONCLUSION

Cancer is one of the leading causes of death worldwide. The primary cause is due to a combination of genetic, epigenetic, and environmental factors. Conventional treatments which have been used ever since such as chemotherapy, radiotherapy, and surgical interventions have been used as the first-line management for cancer, but, their efficacy is often compromised due to factors such as resistance, tumor recurrence, and metastasis.

The recent noteworthy discovery in cancer research is that of cancer stem cells (CSCs). According to the CSC hypothesis, these cells are responsible for tumor relapse and therapy resistance, thus making them important targets for novel therapeutic interventions. CSCs are highly plastic and evade conventional treatment through a dormant status, expression of multidrug resistance proteins, and enhanced DNA repair mechanisms, thus emphasizing the need to stratify this subgroup of patients for novel therapeutic designs. The Notch, Hedgehog, and Wnt pathways are just a few of the many different pathways that are known to control CSC properties. These pathways are required for CSC maintenance, tumor promotion, and therapy resistance. Targeting these pathways by small-molecule inhibitors, monoclonal antibodies, or RNA-based therapeutics has been shown to be promising in preclinical and early clinical studies. The major challenge still remains that CSCs are to be selectively targeted while leaving normal stem cells unscathed, as many of these pathways are also important for tissue homeostasis and regeneration. Recent developments in targeted treatments, Immunotherapeutics, and nanomedicine bring innovative strategies to bear against CSC-driven cancers. The development of CSC-targeting immunotherapies, including chimeric antigen receptor (CAR)-T cell therapy, dendritic cell vaccines, and immune checkpoint inhibitors, has demonstrated encouraging results in certain cancers, particularly hematological malignancies and solid tumors that exhibit a high burden of CSCs. Drugs carried by nanoparticles (liposomes, gold nanoparticles, and quantum dots) can therefore very selectively seek out CSCs and inflict a minimum amount of toxicity to the whole body. Improvements in bioinformatics, artificial intelligence, and single-cell sequencing have greatly enhanced the understanding of the biology of CSCs, they enable the identification of novel biomarkers, characterization of intertumoral heterogeneity, and development of precision medicine strategies tailored to the individual. Even with these recent advances,

challenges remain in determining universal CSC markers, overcoming microenvironmental influences in tumors, and diminishing side effects for therapies targeting CSCs. To further improve the CSC-targeting strategy, future studies must involve a multi-modal therapeutic approach, finalize optimum specificity for the drug, and exploit new technologies to augment treatment results. A combined approach involving targeted therapy, immunotherapy, gene editing, and artificial intelligence-driven predictive models would transform cancer therapy. Continuous efforts to bring together oncologists, molecular biologists, bioinformaticians, and pharmaceutical scientists will ensure the translation of these findings into clinically useful therapies. Overall, CSC targeting is a paradigm shift in oncology, instilling hope for more sustained and effective treatments for cancer. If the scientific and medical community deepens its understanding of CSC biology, streamlines therapeutic approaches, and incorporates cutting-edge technologies, a step toward the realization of long-lasting cancer treatment and improved patient survival rates will be taken. Transform meaningful breakthroughs in CSC-targeted cancers into real victories by fueling translational research, expanding the frontiers of clinical trials, and harnessing the power of precision medicine is the key to paving the road for a transformational treatment option and a future in which cancer would not be a formidable threat.

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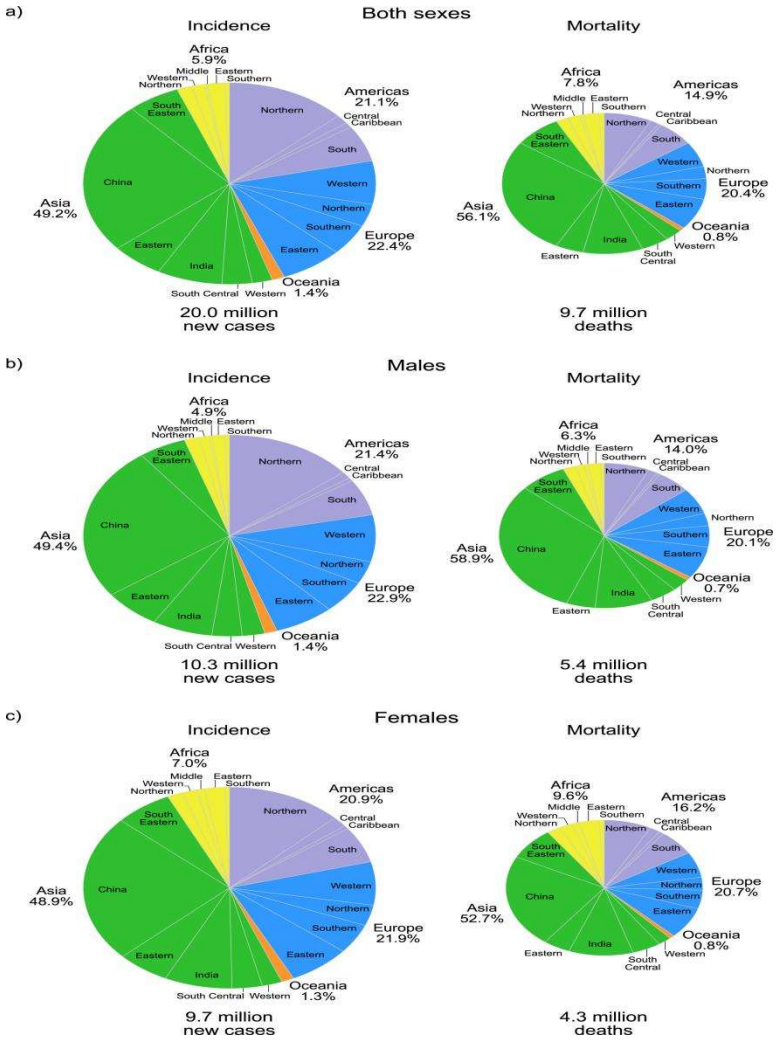
8. APPENDIX

8.1 Appendix A : A series of pie charts showing the incidence and mortality due to cancer worldwide.

Figure 1: Pie charts showing the incidence of cancer and the statistics of mortality due to cancer worldwide.



Description: The pie chart represents the incidence and mortality due to cancer by world area in 2022 for (A) both sexes (B)males (C) females.

9. DISCLOSURE

Acknowledgment

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Ethical approval

Ethical approval was not required for this study

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest