

## A COMPREHENSIVE REVIEW ON CANCER STEM CELLS AND THERAPY

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### ABSTRACT

*Cancer stem cells (CSCs) are a limited but highly tumorigenic subgroup of tumour cells. Which possess unique abilities of self-regeneration, multipotency, and sustained tumor propagation. These cells having a pivotal character to development of cancer, metastasis, therapeutic resistance, and disease recurrence. Unlike bulk tumor population, CSCs exhibit enhanced survival mechanisms, including efficient DNA repair, quiescence, and resistance to apoptosis, making them largely insensitive to conventional treatment modalities such as chemotherapy, radiotherapy, and molecularly targeted therapies. Consequently, residual CSCs can survive treatment, repopulate tumors, and contribute to relapse and poor clinical outcomes.*

*Recent advances in cancer biology have emphasized the importance of selectively targeting CSCs to achieve durable therapeutic responses. This review provides overview of the biological characteristics of CSCs, including their bio-markers, signaling pathways, tumor microenvironment, and mechanisms underlying drug resistance and metastatic potential. Particular attention is given to key signaling networks such as Notch, Wnt/ $\beta$ -catenin, and Hedgehog, which regulate CSC maintenance and survival. In addition, the review highlights emerging therapeutic strategies aimed at eradicating CSCs through biomarker-directed therapies, autophagy modulation, organelle-specific targeting, and drug delivery systems.*

*Nanotechnology-based drug delivery platforms, including nanoparticles, liposomes, and polymeric carriers, have demonstrated considerable selective therapy of anticancer agents to CSCs while minimizing systemic toxicity. These innovative approaches may enhance therapeutic efficacy by overcoming biological barriers and reducing treatment resistance. Overall, targeting CSCs in combination with conventional anticancer therapies offers a promising strategy to suppress tumor recurrence, inhibit metastasis, and improve long-term patient survival. Continued research and clinical translation of CSC-targeted therapies are expected to more effective and personalized cancer treatment strategies.*

**Keywords:** Cancer stem cells (CSCs) · Drug Delivery System, Anti-tumor therapy, Drug-resistance

## INTRODUCTION

Cancer is one of the most serious illness condition in which people suffer from in life. As 2020 data from the WHO indicate, 18.1 million patients and a 9.6 mortality rate will double in 2040<sup>(1)</sup>.

CSCs have the ability to self-renew and generate diverse cancer cell lineages. Several markers and pathways related to gastric cancer stemness have been identified<sup>(2)</sup>. Targeting cancer stem cells is a potential therapy to overcome treatment resistance since cancer stem cells are resistant to a number of chemotherapies.

A subset of cells referred to as CSCs are linked to the development and spread of tumors. Inhibiting the characteristics of cancer stem cells to stop the spread of cancer has been the subject of numerous recent studies.<sup>(3)</sup>

However, the concept of CSCs is widely accepted as important in cancer development, with recent studies demonstrating that cancer stem cells play critical roles in the carcinogenesis of various types of cancer. Several studies have shown that the various components of mixed neuroendocrine-non-neuroendocrine neoplasms are monoclonal, though their molecular signature differs from that of their relative counterparts when they present as separate neoplasms.<sup>(4)</sup>

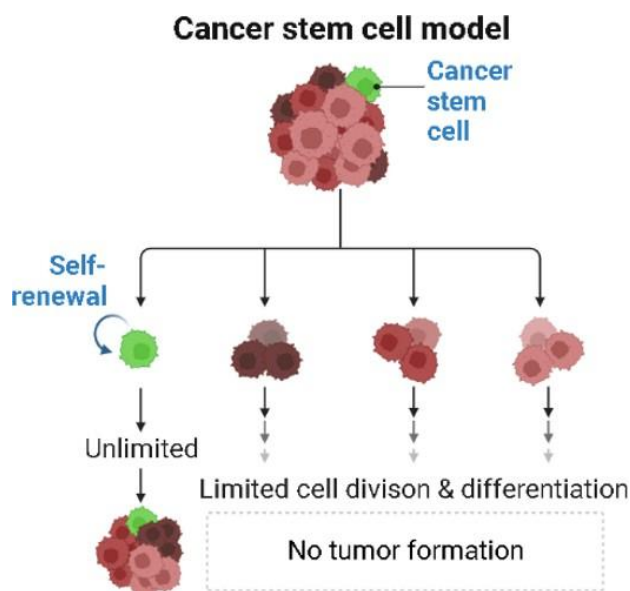


Figure 1: cancer steam cell self-renewal capacity

Hypoxia's role in CSCs seems to be mediated by HIF2a, which is highly expressed in CSCs presented in gliomas and neuroblastomas. Consequently, controlling their activity,

either by decreasing secretion or neutralization by several currently existing agents leads in a significant decrease in CSCs proliferation and self-renewal<sup>(5)</sup>.

Recently, GRN (Granulin-This protein helps regulate the growth, division, and survival of these cells) has been identified as an accurate marker for liver CSCs. GRN, a tumor-stromal interaction factor, plays a significant role in liver metastasis by maintaining self-renewal of hepatic CSCs.<sup>(6)</sup>

The existence of CSCs in colorectal cancer (CRC) is currently under investigation. Following the initial descriptions of CSCs, several studies have investigated its role in human CRC by using immunohistochemical (IHC) analysis to quantify the expression of CSCs biomarkers in tumor samples.<sup>(7)</sup>

In humans, numerous illness phenotypes are caused by inadequate penetrance, yet the underlying molecular mechanism is unclear. For example, cancer stem cells demonstrate inadequate penetrance. Cancer stem cells produce cancer cells at a specific frequency, which is assumed to be owing to secondary mutations that occur in CSCs.

### **Need for drug delivery system in CSc**

In this review article, we main focus to kill the CSc because we are given only medication like the anti-cancer drug like doxorubicin, cisplatin, paclitaxel etc. And some time they give some therapy either photo-thermal, photo-dynamic, immuno-therapy etc. This all methods were so old they only preventing cancer cell but they were not killed the cancer cell. This stem cell was further developed the tumor. So there is not specific target treatment available. In recent review article new drug delivery system developed they directly act on the CSc and kill them so inhibited further development of cancer.

### 1.1 Structure and role CSc

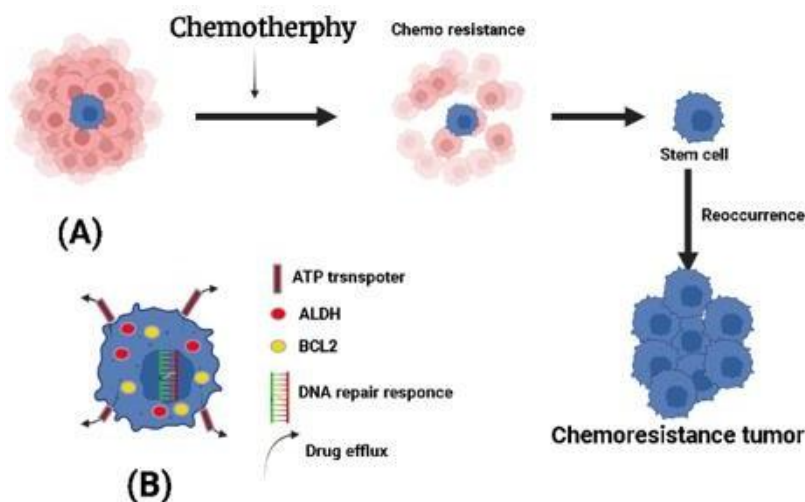


Figure 2:A-cancer stem cell resistance against the chemotherapy, B- structure of cancer stem cell

Furthermore, the most aggressive CSCs are often present in core of the tumor. These cancer stem units induce sustained cancer growth by regulating development, resistance, and metastasis. Therefore, removal of CSCs in tumors through intratumoral injection is currently among the most important goals in cancer research<sup>(8)</sup>.

Although no universal cancer stem cell markers are available to identify individual cancer types, a variety of cancer stem cells, including prostate, brain, and colon, are detected using prominin-1. Following injury, normal lung stem cells help to maintain homeostasis before mutating into cancer stem cells. However, the degree of aggressiveness of cancer stem cells is determined by two factors: migratory ability and proliferation capacity.<sup>(9)</sup>

These cancer stem cells share physiologic features with normal adult stem cells, such as self-renewal and differentiation. Normal stem cells have been proven to be more resistant to cytotoxic chemicals than mature cell types, which is explained by anti-apoptotic mechanisms, quiescence, and high amounts of ATP-binding cassette (ABC) transporters. Cancer stem cells have stem cell properties as well as fast proliferation and considerable treatment resistance.

CSCs are more invasive and resistant to various anti-cancer treatments, and they may be responsible for patient relapse and metastasis. These cells have been seen in a variety of

tumor forms, including CRC (colorectal cancer). Activation of CRC stem cells by AEPX1(Apurinic/Apyrimidinic Endodeoxyribonuclease 1) mediated Jagged1(From Wikipedia, Jagged1 is a cell surface protein that interacts with four receptors in the mammalian Notch signaling pathway. The Notch Signaling Pathway, a highly conserved pathway that functions to establish and regulate cell fate decisions in many organs, has been hypothesized to be the most important cause of chemo-resistance mechanisms <sup>(10)</sup>.

### Drug delivery system in cancer stem cell

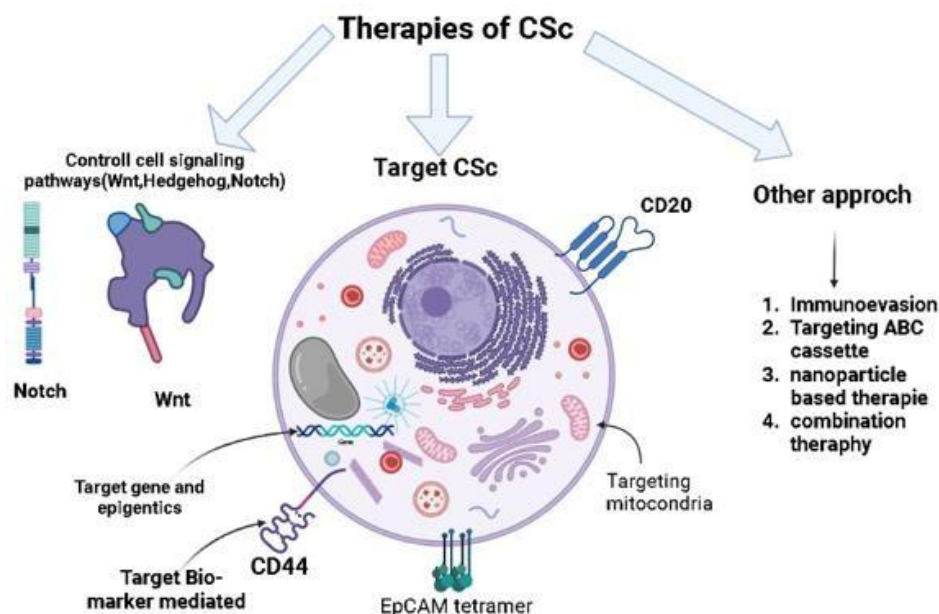


Figure 3: Drug delivery system and therapy against the cancer stem cell

### Control cell signaling pathways

If these CSCs and signaling pathways are better understood, CSC targeting via markers, as well as targeting these aberrant signaling pathways, could provide a new strategy for cancer therapy<sup>(11)</sup>. In mammals, there are more members of the Notch family, which consists mostly of four transmembrane protein receptors (Notch1-4) and five transmembrane protein ligands (DLL1, DLL3, DLL4, Jagged1 and Jagged2)<sup>(11)</sup>. Many signalling pathways in CSCs are disrupted and might be targets for anti-CSC treatments. Overactivation of the Notch pathway has been linked to increased invasiveness of breast CSCs, presumably via affecting EMT <sup>(12)</sup>. Delta-like ligand 4 (DLL-4) is a key component of this pathway, which responsible for stem cell proliferation, regeneration, and development. Any loss in the gene that codes

for DLL-4 has a deadly effect on the vasculature, i.e., abnormalities and overexpression of DLL-4 are identified in tumour vasculature and tumour cells to activate Notch signalling for their future active development<sup>(13)</sup>. The plant-derived medication reduced Notch signalling in both tumour and stem cells, resulting in decreased development of mammosphere, increased protein expression, and reduction of CSC division<sup>(14)</sup>. Apart from that they have shown that blocking Notch signalling makes breast cancer cells more sensitive to **doxorubicin and docetaxel**<sup>(15)</sup>. This signalling pathway may be important in the control of CSC survival, plasticity, and self-renewal. Blocking the Notch pathway with **gamma - secretase inhibitors** can reduce CSC populations, enhance apoptosis, and restrict tumorsphere formation efficiency, a measure of cancer stemness<sup>(16)</sup>. In both in vitro and in vivo forms of Kaposi's sarcoma, blocking Notch activation and inducing apoptosis. A Phase I study in patients with advanced solid tumours found promising anticancer effectiveness in melanoma, sarcoma, and ovarian malignancies, with only minimal adverse effects noted<sup>(17)</sup>.

The Hedgehog signalling pathway may potential role in the development of stem cells. Hedgehog signalling regulates Proliferation and cell fate in embryonic stem cells, but it has also been linked to CSC formation. **Cyclopamine belongs to the piperidines. It was the first Hedgehog antagonist and functions as an inhibitor of glioma-associated oncogenes.** discovered, and its treatment has been shown in a variety of malignancies<sup>(18)</sup>. In a chronic myeloid leukaemia model, cyclopamine decreased CSCs and caused tumour regression, slowed tumour development in a medulloblastoma model, and reduced pancreatic CSC proliferation<sup>(19)</sup>. Cyclopamine, a very effective Hedgehog signalling blocker, suppresses breast cancer development in the absence of SMO (Smoothed). In ovarian cancer, inhibiting hedgehog signalling resulted in natural cell death and decreased its viability, migration, and invasion<sup>(20)</sup>. These findings suggested prohibit the Hh pathway might be used as a therapeutic strategy for ovarian cancer. Then we looked into the connection between DHA (Dihydroartemisinin) and the Hh pathway. The analysis of the signalling mechanisms that drive hepatocarcinogenesis is a novel target for HCC therapy<sup>(21)</sup>. The Hedgehog (Hh) signalling system promotes the growth of several human cancers, including HCC, breast cancer, and basal cell carcinoma. In HCC, the Hh pathway plays an important role in carcinogenesis, invasiveness, recurrence, and CSC maintenance<sup>(22)</sup>. **5-FU** therapy may suppress Shh signalling expression and impede motility in hedgehog-activated HCC cell lines. These findings imply that the combination of 5-FU and chemotherapy with an inhibitor of the Shh signalling system might be a potential therapeutic strategy for HCC<sup>(23)</sup>.

Hedgehog aberrations are associated with altered Wnt pathway activation. Wnt is thought to have a function in the maintenance of CSC self-renewal capacity. CD44, a CSC marker, is a key Wnt signalling target. As a result, targeting the Wnt/catenin signalling system might be a important technique for chemoprevention and treatment in breast cancer. In fact, growing research suggests that natural dietary substances like as sulforaphane and **curcumin** suppress breast CSCs and downregulate the Wnt/catenin self-renewal pathway<sup>(24)</sup>. We co-treated colorectal CSCs with LiCl and PEITC (Phenethyl isothiocyanate) to confirm inhibitory effects of PEITC on colorectal CSCs. LiCl is a typical Wnt/catenin pathway activator that has been frequently utilized to stimulate the Wnt/catenin pathway. PEITC suppressed colorectal CSCs by inhibiting the Wnt/catenin signalling pathway<sup>(25, 26)</sup>. Overexpression of Let-7c miRNA, an oncosuppressive miRNA capable of inhibiting CSC-associated traits, was found to increase tamoxifen sensitivity by impairing the ER-dependent activation of the Wnt signaling pathway, in accordance with the crosstalk between dysregulated Wnt signaling and tamoxifen resistance in ER+ BC<sup>(27)</sup>.

| Pathway       | Therapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Reference                                                                                |
|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Notch pathway | <ul style="list-style-type: none"> <li>➤ Plant derived medication- Reduce notch in both ways bulk tumor and CSC decrease mammosphere development.</li> <li>➤ Doxorubicin and Docetaxel- Block this pathway in breast cancer. CSCs are more sensitive to these two drugs.</li> <li>➤ Gama secretase inhibitor- Reduce CSC population, enhance apoptosis and restrict tumor sphere formation. In both in-vivo and in-vitro Kaposi's sarcoma blocking notch and induce apoptosis. Phase I study in patient produce anticancer activity and minimal adverse effect.</li> </ul> | <ul style="list-style-type: none"> <li>• (28)</li> <li>• (29)</li> <li>• (30)</li> </ul> |

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|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| <b>Hedgehog pathway</b> | <ul style="list-style-type: none"> <li>➤ Cyclopamine (glioma- associated oncogene inhibitor): They was the first antagonist discovered and its effects have been explored variety of malignancies.</li> <li>➤ Cyclopamine decrease CSc and tumor regression. There are hedgehog signaling pathway blocker.</li> <li>➤ 5-FU therapy may suppress Shh signaling expression and impede mortality hedgehog – activated Hcc cell lines</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                           | <ul style="list-style-type: none"> <li>• (31)</li> <li>• (32)</li> <li>• (33)</li> </ul> |
| <b>Wnt pathway</b>      | <ul style="list-style-type: none"> <li>➤ CD44, a CSc marker is a key Wnt signaling target.</li> </ul> <p>Sulforaphane and curcumin-Suppress breast CSc and down regulate the Wnt/catenin self- renewal pathway</p> <ul style="list-style-type: none"> <li>➤ Colorectal cancer CSc co-treated with LICL and PEITC (Phenethyl isothiocyanate) confirm the role of Wnt/catenin pathway inhibitory</li> <li>➤ LICL- Typical Wnt/catenin pathway activator that has been frequently utilized to stimulate the Wnt</li> <li>➤ PEITC (Phenethyl isothiocyanate)- Supressed colorectal CSc by inhibiting the Wnt/catenin signaling pathway</li> <li>➤ Overexpression of Let-7c miRNA, an oncosuppressive miRNA capable of inhibiting CSC-associated traits, was found to increase tamoxifen sensitivity by impairing the ER-dependent activation of</li> </ul> |                                                                                          |

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|--|-----------------------------------------------------------------------------------------------------------------------------------|--|
|  | the Wnt signaling pathway, in accordance with the crosstalk between dysregulated Wnt signaling and tamoxifen resistance in ER+ BC |  |
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Table 1: Treatment of cancers stem cell by inhibiting the signaling pathways

### DDs autophagy-mediated targeting

Autophagy is a catabolic mechanism that promotes tumour cell survival and treatment resistance by forming autophagosomes<sup>(34)</sup>. Autophagy is an important survival factor in cancers with abnormalities in apoptotic signalling pathways, and CSCs have a high degree of autophagy, which contributes to their longevity and resistance to treatment<sup>(35)</sup>. The study of how selective autophagy targets certain organelles or proteins, on the other hand, has given rise to terminology like mitophagy, pexophagy, and xenophagy. Autophagy has recently been recognised as a therapeutic target in a variety of disorders, including cancer<sup>(36)</sup>. Some evidence shows that autophagy may promote apoptosis in breast and pancreatic CSCs via different molecular pathways<sup>(37)</sup>. According to existing research, autophagy appears to serve a dual function in mediating **sorafenib's** anti-thyroid cancer activity. Unlike sorafenib and **pigenetic**, which have many targets, apatinib is a TKI that specifically targets vascular endothelial growth factor receptor 2. (VEGFR-2)<sup>(38)</sup> We then looked for a suitable medication that may interfere with autophagy and induce cytotoxicity in order to target the Achilles' heel of CSCs. We chose TZ, an antipsychotic antagonist of the DRD2 dopamine receptor that has been studied in CSCs from myeloid leukaemia, glioblastoma, lung, liver, ovarian, and breast malignancies as a repositioning medication<sup>(39)</sup> TZ has also been characterised as an autophagy inducer in glioblastoma, ovarian, cervical, and melanoma cancer cells<sup>(40)</sup> Targeted treatment is an important method for reprogramming CSCs to become regular stem cells. Targeting autophagy in particular is a promising technique for controlling CSCs. Although certain chemotherapies cause autophagy stimulation. Autophagy has an important therapeutic role in many malignancies by promoting the initiation of immunogenic cell death and clearance.<sup>(34)</sup> However, inhibiting autophagy by targeting BECN1 (beclin1) can restore CTL-mediated tumour cell lysis without compromising mesenchymal morphology or EMT marker expression<sup>(41)</sup>. Furthermore, autophagy can enhance GZMB and synaptic GJA1/connexin 43 degradation in tumour cells, leading to reduced tumour cell sensitivity to NK-mediated lysis under hypoxia, while autophagy blocking can restore NK cell-mediated cell lysis<sup>(42)</sup>. As a result, inhibiting autophagy has emerged as a potential immunotherapeutic

method for preventing cancer cell immune escape. The use of nano-particulate delivery devices target autophagy in CSCs is an interesting route for therapy. Nano carrier-mediated autophagy suppression, for example, significantly decreased the “stemness” of human BCSCs and increased their sensitivity to chemotherapeutics<sup>(43)</sup>. Furthermore, combining AgNPs with salinomycin was discovered to have a synergistic effect in triggering apoptosis and autophagy in ovarian cancer cells<sup>(44)</sup>.

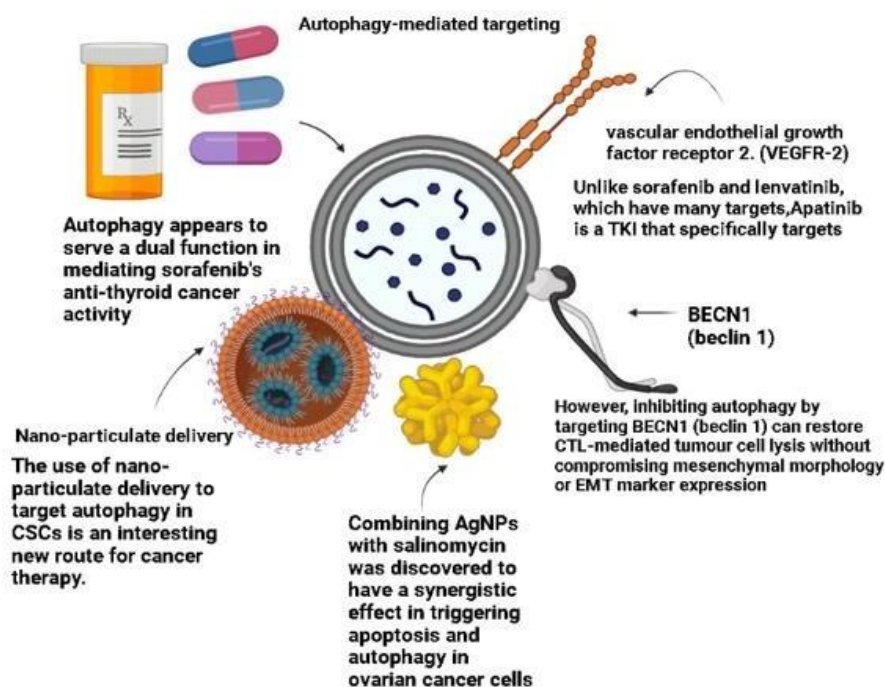


Figure 4: Autophagy-mediated targeting of the cancer stem cell (CSc)

## TARGETING CSC BIO-MARKER MEDIATED

CSC stemness is promoted by both internal and external cues, such as molecular pathways, surrounding niches, and transcriptional factors. CSCs were originally identified via surface marker expression, and various surface and internal CSC biomarkers have been investigated to date to filter CSCs from heterogeneous cancer cells. Many surface markers, including CD133, CD44, and EpCAM, have been identified as possible CSC indicators in a variety of solid and non-solid tumour<sup>(45)</sup>. These transmembrane surface biomarkers have been identified as a significant therapeutic target for eliminating CSC treatment resistance in several forms of cancer<sup>(46)</sup>. Targeting CSC surface markers is one possible CSC therapies method. CD44, a cell-surface extracellular matrix receptor, is one of the most well-established and widely

utilized CSC indicators <sup>(47)</sup>. Many research portrayed CD44 antibody treatment as the primary anti-CSC strategy. The first of these investigations demonstrated that H90 antiCD44 treatment completely eliminated AML <sup>(48)</sup>. CD133 is a transmembrane glycoprotein that has been identified as a CSC marker in a variety of malignancies including glioblastoma, hepatocellular, and colon cancer. Because of their delayed cell cycle, decreased proliferation, and increased expression of DNA repair and antiapoptotic genes, CD133+ CSCs have demonstrated resistance to chemotherapy and radiation <sup>(49)</sup>. Using a proteasecleavable linker, the AC133 antibody was attached to a strong cytotoxic agent, monomethyl auristatin. This antibody drug conjugate was rapidly absorbed, co-localized with the lysosome, and shown strong anti-hepatocellular cancer cell efficacy <sup>(47)</sup>. EpCAM has been identified as a CSC marker in solid tumour and is associated with all CSC features. In breast cancer, the EpCAM+/CD44+/CD24- population had a considerably greater frequency of tumor initiating cells. Furthermore, ovarian cancer cells with strong EpCAM expression were implicated in EMT, which resulted in metastasis. Humanized EpCAM antibodies have shown substantial anti-tumor efficacy in preclinical and early clinical investigations <sup>(50)</sup>.

#### DDS FOR TARGETING CSC ORGANELLES

The mitochondrion is one of the most important organelles, because it participates in the entire process of cell fate determination and development, from cell self-movement to cell signalling and death of cells <sup>(51, 52)</sup>. As previously stated, CSCs exhibit abnormalities in metabolism, proliferation, and apoptosis. As a result, it is not surprising that CSCs appear to undergo pathological reprogramming, particularly mitochondrial function remodelling. Because of mitochondria's role as a central hub, anti-CSC therapeutic strategies targeting mitochondria have been developed. Studies on the in-depth understanding of mitochondrial biology in CSCs have been carefully developed <sup>(53)</sup>. Similarly, the drugs that can effectively target mitochondrial functions do <sup>(54)</sup>. Many studies have centered on the successful implementation of mitochondria-targeted delivery. It was determined whether serum protein-coated Au NRs had a beneficial effect on carcinoma cells. Because of their enhanced liposome membrane permeation ability, reduced cancer cell efflux, and exceptional lysosomal to mitochondrial transfer ability, the Au NRs effectively targeted mitochondria. The parallel molecular mechanism and in vitro cytotoxicity were determined, and the results revealed decreased mitochondrial membrane potential, increased oxidative stress, and decreased cancer cell viability. These findings have important implications and provide

guidance for the development of mitochondrion-targeted anti-tumor therapy<sup>(55)</sup>. Dequalinium on the liposome surface was used as a targeted modification in mitochondria-targeted quinacrine liposomes. As a result of the mitochondrial membrane with dequalinium's positive charge and delocalized charge centre, the dequalinium-modified quinacrine liposomes were enriched in the mitochondria of living cells<sup>(56)</sup>. which developed a targeting berberine liposome using a mitochondria-tropic functional material conjugated by dequalinium and carboxyl polyethylene glycol distearoylphosphatidylethanolamine (DQA-PEG2000- DSPE). The targeting berberine liposomes were properly transported across CSCs and selectively assembled in the mitochondria, resulting in increased cytochrome C release and further apoptosis of breast CSCs. Dox is an anti-cancer drug that intercalates into DNA and inhibits Topoisomerase II progression, resulting in cell death. Furthermore, Dox derivatives have been shown to interact with mitochondria by disrupting major mitochondrial functions, causing membrane-bound proteins and enzymes to be damaged. Cisplatin binds to nuclear DNA and causes DNA cross-linking, and some studies have shown that it can also interact with mitochondrial DNA<sup>(57)</sup>.

## CONCLUSION AND FUTURE PERSPECTIVES

Recent thorough refinement and advancement of tumour therapy techniques has resulted in significant tumour control and increased patient survival. Nevertheless, these treatments are only temporary control measures for metastases and primary tumours, and patients who get them have a significant risk of recurrence and metastasis, which is ultimately due to the ineffective removal of CSCs. As a result, there has been a lot of interest in developing therapy regimens that specifically target CSCs, as well as DDSs and carriers. We systematically discussed various DDSs for CSC-targeted treatments in this review. The aforementioned DDSs and carriers successfully improved the linked medications' deficiencies in terms of their physical and chemical properties, improved drug targeting and pharmacological activities, and decreased the frequency of adverse effects that leading to size reduction. However, there is still much work to be done before these tactics may be used in clinical settings. Future research should concentrate on the following areas: More innovative drug delivery systems should be created in order to harness the synergistic therapeutic effects of combining medications. Because to CSCs' strong resistance, high metastatic potential, and complex niche, achieving synergy requires the combination of two or more targets. The most popular co-delivery drug systems, however, concentrate on straightforward co-loading

and ignore the pharmacokinetic properties, inhibitory effects, release characteristics, and drug-drug interactions of the various drugs within the carriers, which makes it challenging to achieve synergistic effects. The corresponding carrier must be improved to release medications at the correct site to ensure optimal efficacy and cause the fewest negative effects. The target positions of each drug, such as CSC organelles and niches, differ. The more effective carriers should concurrently attack CSCs and cancer cells. According to the "seed-soil" theory, CSC spread, moved to a different niche that was suitable and had characteristics of their original niche, and then established their own niche again. The current CSC niche helps CSCs survive, and the right niche in the distance encourages the transfer of CSCs. The two procedures compliment one another and work to advance one another. Moreover, CSCs can develop into cancer cells and cancer cells can be made to change into CSCs, creating a dynamic process of reciprocal equilibrium. Hence, in order to effectively treat cancer, it is necessary to simultaneously target and eradicate both cancer cells and CSCs, as well as the CSC niche. Since there aren't many CSCs in cancer tissue, it's best to eradicate a lot of the other cancer cells that are already there before focusing on the exposed CSCs. Understanding the underlying pathophysiology of cancer in each patient is essential in the context of customised medical practises and the complicated causes of CSCs so that the proper corresponding medicine or strategy and drug delivery system may be recommended for each individual. Undoubtedly, CSC-targeted DDSs would advance more with the advancement of DDSs and the introduction of more drug delivery vehicles in the future.

## **AUTHORS' CONTRIBUTION**

The authors declare that they have no known competing interests or personal relationships that could have appeared to influence the work reported in this paper.

## **DECLARATIONS:**

### **Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### **Data Availability Statement**

The authors confirm that the data supporting the findings of this study are available within the article.

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