

AN OVERVIEW OF THERAPEUTIC INFERENCES AND CHALLENGES IN TARGETING CANCER STEM CELLS

MANASH BHAKTA^[1], DR. ANIL MIDDHA^[2]
Department of Pharmacy
^[1,2]OPJS University, Churu (Rajasthan) – India

Abstract

Cancerstem cells (CSCs) have been recognized as uncommon cell populaces in numerous diseases, including leukemia and strong tumors. Aggregating proof has proposed that CSCs are equipped for self-reestablishment and separation into different sorts of tumor cells. Distorted control of quality expression and some flagging pathways has been seen in CSCs contrasted with other tumor cells. CSCs are thought to be in charge of tumor start, movement, metastasis, repeat and medication resistance. The CSC theory has as of late pulled in much consideration because of the potential for disclosure and advancement of CSC-related treatments and the recognizable proof of key particles required in controlling the novel properties of CSC populaces Novel mixes and remedial techniques that specifically target CSCs have been recognized, some of which have been assessed in preclinical and clinical reviews. In this article, we audit new discoveries identified with the examination of the CSC speculation, and talk about the pivotal pathways required in directing the improvement of CSC populaces and the advances in investigations of medication resistance. What's more, we survey new CSC-focused on helpful systems intending to annihilate malignancies.

Keywords: *cancer; stem cell; leukemia; biomarker; ATP-binding cassette transporter; signaling pathway; tumor microenvironment*

1. INTRODUCTION

The cancer immature microorganism is characterized by two vital attributes. This experiences self-restoration division. It is an unbalanced division in which a precise is created with formative potential

indistinguishable to its growth stem cell. Second trademark is the creation of the little girl or "forebear" cells.

They at first hold a number of attributes of their parent growth undeveloped cell however successively lose their self-recharging

potential with each ensuing cell division as they separate to produce develop cells of no less than one yet regularly numerous cell sorts inside an organ[1]. A one of a kind microenvironment is found in the disease undeveloped cell specialty which is the required for immature microorganism work.

Secluding stem organisms from the undeveloped cell specialty may change their capacity, and this should be considered when contemplating immature microorganism's in vitro and in vivo circumstances. Foundational microorganisms additionally assume a vital part in tissue repair and homeostasis. This is real contrasts between substantial or tissue undeveloped cells and cancer foundational microorganisms. Substantial stem organisms create typical tissues in an exceedingly controlled process, while cancer undeveloped cells deliver tumors.

2. THE CONTROVERSIAL CANCER STEM CELL MODELS

Most tumors are thought to emerge from one single cell that forms into a heterogeneous populace. In any case, two particular models have been proposed to represent tumor development and the heterogeneity inside tumors. In the cancer immature microorganism demonstrate, the modalities of

tumor, for example, start, movement, metastasis and repeat, depend fundamentally on uncommon undeveloped cells. The heterogeneity and progressive system between the greater part of the cells inside a tumor result from deviated division of CSCs. This model proposes that tumors are profoundly progressive with a one of a kind self-reestablishing populace of cells at the highest point of the chain of importance. Every single other cell including the tumor mass are gotten from separated CSCs.

Be that as it may, an option see additionally exists, called the clonal advancement demonstrate (CE model)[2]. This model sets that all tumor cells add to tumor upkeep with contrasting limits. The intercellular variety is principally credited to subclonal contrasts that outcome from hereditary or potentially epigenetic changes amid disease advancement.

These reviews have demonstrated that tumor immature microorganisms exist however may develop after some time. A hereditary clone offers ascend to no less than two clonal genealogies that develop autonomously, with each clone obtaining different hereditary abnormalities; one clone rises as the prevailing indicative clone, while the other clone offers ascend to the prevalent clone

containing extra changes at relapse[3].

3. CHARACTERISTICS OF CANCER STEM CELLS

CSCs are particular populaces of tumor cells. CSCs have numerous one of kind elements that make them be imperative for tumor arrangement. CSCs can self-restore and are undying and important to keep up the number of inhabitants in tumor cells. CSCs are pluripotent and can produce tumor cells with various phenotypes, which brings about the development of the essential tumor and rise of new tumors.

CSC biomarkers

Because of the cozy relationship amongst CSCs and tumor start, movement, metastasis and medication resistance, the disconnection of these cells from the aggregate growth cell populace is fundamental for definite reviews. Unmistakable and particular surface biomarker phenotypes can be utilized to recognize CSCs from other tumor cells and ordinary stem cells. As of now, the most widely recognized technique used to distinguish CSCs is fluorescence-actuated cell sorting (FACS) in view of cell surface markers or intracellular particles [4].

The leukemia foundational microorganism (LSC), w CD34+CD38– surface marker

phenotype, and best comprehended sort of CSC]. The loss of CD38 recognizes LSCs from typical hematopoietic immature microorganisms (HSCs), albeit both LSCs and HSCs are CD34+[3]. In this manner, more particular surface markers of LSCs have been found, and blends of these markers have been utilized. For instance, the mix of CD34+CD38 – HLA-DR–CD71–CD90– CD117–CD123+ is remarkably present on the surface of LSCs yet not on typical HSCs][5].

With respect to malignancies, Al-Hajj et al have distinguished ESA+CD44+CD24–/low Lineage– cells as bosom growth stem organisms. The creators found that contrasted with other cell populaces, this populace has a more noteworthy limit with respect to tumor development in NOD/SCID mice. Furthermore, Singh et al have found that transplantation of a little number of CD133+ mind growth cells can produce tumors in NOD/SCID mice, recommending that CD133 may be a vital CSC marker [6].

Albeit awesome advance has been made in comprehending CSC surface particles, any issues still stay to be tended to. Here, we compress incomplete phenotypes of CSC markers as per the cancer sorts (Table 1).

Table 1: Cell surface phenotypes of CSCs

Tumor type	Phenotype of CSCs markers
Leukemia	CD34 ⁺ CD38 ⁻ HLA-DR-CD71 ⁻ CD90 ⁻ CD117 ⁻ CD123 ⁺
Breast cancer	ESA ⁺ CD44 ⁺ CD24 ^{-/low} Lineage ⁻ , ALDH-1 ^{high}
Liver cancer	CD133 ⁺ , CD49f ⁺ , CD90 ⁺
Brain cancer	CD133 ⁺ , BCRP1 ⁺ , A2B5 ⁺ , SSEA-1 ⁺
Lung cancer	CD133 ⁺ , ABCG2 ^{high}
Colon cancer	CD133 ⁺ , CD44 ⁺ , CD166 ⁺ , EpCAM ⁺ , CD24 ⁺
Multiple myeloma	CD138 ⁻
Prostate cancer	CD44 ⁺ , $\alpha 2\beta 1$ ^{high} , CD133 ⁺
Pancreatic	CD133 ⁺ , CD44 ⁺ , EpCAM ⁺ , CD24 ⁺
Melanoma	CD20 ⁺
Head and neck cancer	CD44 ⁺

ATP-binding cassette

ATP-restricting tape (ABC) transporters are layer transporters that can pump different unmistakable and fundamentally disconnected little particles, (for example, cytotoxic medications and colors) out of cells to the detriment of ATP hydrolysis. Typical stem cells and cancer undeveloped cells seem to express large amounts of ABC transporters. This marvel could add to multidrug resistance (MDR) in light of the fact that numerous anti-tumor medications can be pumped out, in this way bringing about low intracellular medication fixations. Hence, the raised levels of ABC transporters empower tumor

immature microorganisms to oppose current growth treatments. The notable "sparkling stars" of the ABC superfamily incorporate multidrug resistance proteins (MRPs/ABCC), bosom cancer resistance protein (BCRP/ABCG2) and P-glycoprotein (P - gp/ABCB1). High expression levels of ABC transporters in threatening immature microorganisms can be controlled by treatment of cells with Hoechst 33342 color. Uncommon cells containing elevated amounts of the ABC transporters expulse Hoechst; this part is assigned as side populace (SP) cells. Aggregated information have demonstrated that various cell lines and tumors contain SP cells and that this cell populace has aMore

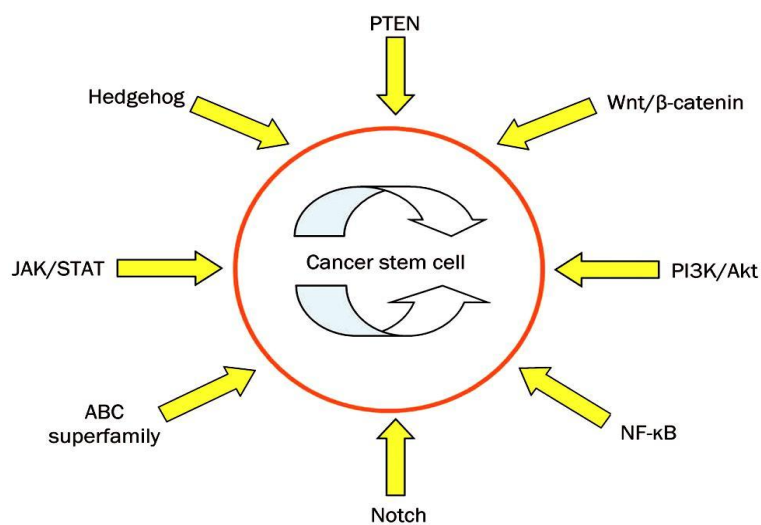
prominent limit with regards to tumor genesis than non-SP cells [7].

Key signaling pathways

Dysregulation of signaling pathway networks plays an important role in enabling CSCs to retain stem cell proper-ties. As shown in

Figure 1, the pathways and elements that are involved in the control of self-renewal and differentia-tion of cancer stem cells and normal stem cells include PI3K/Akt, PTEN , JAK/STAT, Wnt/ β -catenin, hedgehog, Notch, NF- κ B, Bcl-2, and others [8].

Figure 1:Signal pathways related with cancer stem cells



Atomic variable kappa B (NF- κ B), a translation component that directs the outflow of different qualities, takes an interest in various cell reactions to boosts, for example, cytokines, microbial antigens, free radicals and bright irradiation[9]. An expanding assemblage of confirmation has demonstrated that NF- κ B influences the declaration of a few apoptosis-related proteins, for example, Bcl-xL, Bcl-2, survivin, cell inhibitors of apoptosis (cIAPs), TRAF and cell cycle administrative

segments. Unusual NF- κ B actuation causes growth improvement and movement, chemoresistance, perpetual irritation and immune system infections.

The notable Notch, Hedgehog and Wnt flagging way ways assume major parts in keeping up CSC populaces. Score flagging influences self-recharging and ancestry particular dif-ferentiation of ordinary human bosom immature microorganisms. Additionally, Notch4 action is raised in bosom

CSCs, and repressing Notch4 movement can diminish the bosom CSC populace, in this manner smothering tumor start[10].

4. THERAPIES TARGETING CANCER STEM CELLS

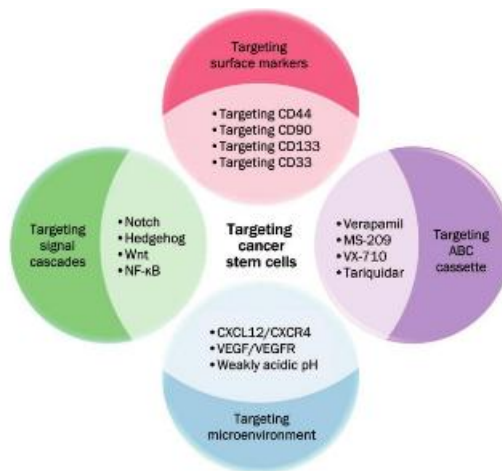
Current restorative techniques against tumor have serious limi-tations that as often as possible prompt to treatment disappointment. A typical reason for treatment disappointment in various malignancies is resis-tance to chemotherapy and radiotherapy. Likewise, numerous systems that are not adequately particular against CSCs can be harmful to solid tissues, and patients as a rule face the danger of repeat and metastasis on the grounds that most treatments can't take out CSCs[11].

As of late, various novel helpful frameworks have been outlined with the point of executing CSCs and changing the microenvironment (specialties) supporting these cells. Both unobtrusive surface marker contrasts and changes in flag ing pathways are appealing restorative targets. Researchers have recognized numerous potential CSC restorative targets, including the ABC super

family, hostile to apoptotic elements, detoxifying proteins, DNA repair chemicals and unmistakable oncogenic falls.

Targeting cellular surface markers

Markers differentially communicated between typical stem cells and CSCs, including CD44, IL-3R, and the immunoglobu-lin mucin TIM - 3, have been used to explicitly target leukemia undeveloped cells in human AML. For each situation, treatment with antibodies against these phone surface atoms dramati-cally diminishes leukemogenicity and kills CSCs in mice. Antibodies against CD47, which is communicated at much larger amounts in ALL than in typical cells, may likewise adequately execute leukemia stem organisms. In treating MCF-7 bosom growth, a hostile to CD44 counter acting agent conjugated gold nanorod has been utilized to target and photograph remove CD44+ cells, which show huge cancer foundational microorganism qualities. Utilizing this approach, focused on cells assimilate close infrared light, which brings about expanded neighborhood temperature at the assigned area [12].

Figure 2: Therapies targeting cancer stem cells**Targeting ATP-driven efflux transporters**

Antitumor medication efflux brought on by ATP - driven pumps is the essential explanation behind chemo resistance. Specialists have planned various techniques to dodge, kill or even endeavor tranquilize efflux pumps to defeat sedate resistance. A few pharmacological operators that can associate with ABC trans-doormen have been created to restrain multidrug resistance[13].

The primary P-gp efflux pump inhibitor to be recognized was verapamil, which is regularly utilized as a part of SP examination to obstruct the rejection of Hoechst color. Concurrent treatment with verapamil and antitumor medications, for example, Dox, paclitaxel or vincristine, has shown promising helpful impacts.

Khdair et al have conveyed methylene blue (a kind of P-gp inhibitor) and Dox all the while into BALB/c mice bearing syngeneic JC adenocarcinoma tumors. Uniquely expanded amassing of medications inside the sore, upgraded tumor cell apoptosis, stifled cancer cell expansion, disabled tumor development and fundamentally enhanced creature survival were watched.

An option technique focusing on ABC transporters includes managing the protein expression levels of these vehicle ers. Sims-Mourtada et al have demonstrated that Hedgehog flagging can control the declaration of MDR1 and ABCG2. The expression levels of ABCG2 and MDR1 are downregu endless supply of PC3 cells with cyclopamine (a SMO flagging component inhibitor), and focused on knockdown of ABCG2 and MDR1 expression

by siRNA somewhat turns around chemoresistance.

Targeting key signaling cascades

Dynamic against apoptotic pathways and parallel idle genes apoptotic pathways are additionally problem areas pulling in analysts. Monoclonal antibodies focusing on Notch flagging have indicated appealing prospects. Hindrance of Notch1 can fundamentally diminish the CD44+CD24-/low subpopulation and lower the occurrence of cerebrum metastases from a bosom cancer cell line.

Large amounts of β -catenin have been depicted to connect with CSC tumorigenicity in colon cancer. A few pharmaceuticals are under scrutiny as inhibitors of Wnt flagging. Monoclonal antibodies against the Wnt course have been tried with promising hostile to tumor movement.

A few gatherings have found that repressing NF- κ B can significantly smother chemoresistance, and inhibitors focusing on NF- κ B can intervene antitumor reactions and upgrade the affectability of tumor cells to anticancer medications. Synchronous conveyance of DOX and the NF- κ B inhibitor PDTC effectively overcomes multidrug resistance. Ganta and Amiji have additionally watched improved cell apoptosis upon

treatment with paclitaxel and curcumin, another NF- κ B inhibitor. Curcumin can hose the protein levels of MDR1 and actuate apoptosis way ways, subsequently weakening the limit with respect to multidrug resistance [14].

Moreover, IL-4 can secure the tumorigenic CD133+ CSCs in human colon carcinoma from apoptosis. In this way, against IL-4 immunizer or IL-4Ra foe can make CSCs get to be apoptotic and uniquely sharpen CSCs to chemotherapeutic medications.

Targeting the tumor microenvironment

The tumor microenvironment can make a specialty to nurture and shield CSCs from medication initiated apoptosis. For instance, most develop B-cell malignancies are serious. Convincing proof has recommended that frill stromal cells in the tissue microenvironments of bone marrow and optional lymphoid organs support infection movement by advancing dangerous B-cell development, multiplication and medication resistance. One case is the collaboration between stromal cell-inferred figure 1 (SDF-1/CXCL12), discharged by bone marrow stromal cells, and its receptor CXCR4[40]. CXCR4 can manage leukemia cell trafficking and homing deep down marrow microenvironment, where discharged CXCL12

guarantees that leukemia cells nearly contact the marrow stromal cells, therefore activating cell development and chemo resistance signals. CXCR4 antagonists, for example, Plerixafor (AMD3100) and T14003 analogs, can harm glue tumorstroma collaborations and initiate leukemia cell assembly far from the bone marrow stromal microenvironment, bringing about the phones to end up distinctly more vulnerready to cytotoxic medications. The novel approach of focusing on the CXCR4-CXCL12 pivot is being investigated in clinical trials for leukemia.

Tumor angiogenesis has likewise been accounted for to be identified with CSC survival and medication resistance. VEGF has been perceived to correspond with microvasculature development and tumor development. Calabrese et al have treated mice bearing U87 glioma cell xenografts with bevacizumab and watched diminished microvasculature thickness and tumor development. The creators likewise watched a decrease in the quantity of CD133+/nestin+ tumor-starting cells. The blend of the VEGFR2 immune response DC101 and the cytotoxic specialist cyclophosphamide is likewise more powerful against C6 gliomaxenografts in vivo than individual operators alone[15].

5. CONCLUSION

Convincing proof has demonstrated that CSCs in fact exist in different malignancies and show capacities with regards to self-renewal and separation that are basic for tumor start, movement, metastasis and repeat. As of now, the ID and disengagement of CSCs are basically in light of CSC surface markers. Nonetheless, CSC markers are not universal, and CSC populaces have over and again been refined because of the distinguishing proof of new markers. In this way, to what degree will an appropriate number of producers be recognized to characterize the genuine population of CSCs? Would these biomarkers change amid cancer movement? These inquiries still stay to be tended to. Planning novel ways to deal with target CSCs has gotten much consideration in the course of recent years. Expanding evidence has proposed that a far reaching procedure may enhance disease medications. For instance, a nanoparticle conjugated to the accompanying four pivotal components has been planned:

1. a molecule (*ie*, ligand) targeting a specific CSC;

2. a cytotoxic anticancer drug to eliminate CSCs;
3. a chemo-sensitizer to overcome drug resistance (such as an ABC trans-porter inhibitor); and
4. an imaging agent to facilitate tumor diagnostics. Such a combination would exert the anti-tumor effect more specifically and powerfully with fewer side-effects.

Furthermore, this approach would enable accurate identification of the localization of the primary tumor and its metastases. The rise of the cancer stem cell hypothesis broadens our horizons and provides a new approach to eradicate malignancies. However, the identification of strategies that exploit the unique characteristics of CSCs requires further study and the cooperation of multidisciplinary areas.

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