IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

Human Journals
Review Article
November 2018 Vol.:11, Issue:1

Cancer Stem Cells and Its Resistance towards Therapies

IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

Hewa Kularathnage Sanduni Lakshika[1], Nivethika Sivakumaran[2*]

[1] Department of Bio Medical Science, International Collage of Business and Technology, No 36, De Kretser Place, Bambalapitiya, Colombo 4, Sri Lanka

[2] School of Science, Edulink International Campus, No 6, Glen Aber Place, Bambalapitiya, Colombo 04, Sri Lanka.

Submission: 21 October 2018
Accepted: 27 October 2018
Published: 30 November 2018

Keywords: CSCs, Metastasis, Therapy resistance, Signaling pathways, Tumorigenicity

ABSTRACT

Study on cancer stem cells (CSC) has been attracted researchers' attention from the beginning of the 21st century because cancer is a large health problem in worldwide. This study hopes to get an improved understanding on CSCS and their characteristics, mechanisms and the therapies targeting them. CSCs have some key characteristics like self-renewal, tumorigenicity, differentiation and resistant to drugs. Under mechanism and regulation of CSCs there are some major signaling pathways were explained. The current treatments such as chemotherapy and radiotherapy responsible to target tumor bulk and not to cancer stem cells. There also some therapies such as surgery, hormonal therapy, anti-angiogenesis therapy, immunotherapy and natural therapies. Identification of surface markers and their molecular features which associated with CSC phenotype may help with the design of effective treatments recently.

INTRODUCTION

Cancer is a major cause of mortality in the world. CSCs are derived from normal stem cells, differentiated cells and progenitor cells during their cell division from different types of mutations. Cancer stem cells are involved in both initiate the tumors (cancers) and contribute to tumor resistance on treatments [1].

From the study on hematopoietic stem cells (HSCs) can get a proper understanding about cancer stem cells because both normal stem cells and cancer cells from hematopoietic system is well characterized [2]. There are major similarities between normal stem cells and tumorigenic cells such as long lifespan, resistance to drugs and toxins, resistance to apoptosis. Both of the cells have comprehensive proliferative potential and the ability to give rise to new tissues, composed by heterogeneous proliferative potentials. CSCs differ mainly from normal stem cells in their tumorigenic activity [3].

CSCs have some main key characteristics. Morphological diversity of cells can visible under a microscope and there are differences among tumour cells in a phenotype such as expression of surface antigens and cytoplasmic proteins, activity of biochemical processes [3]. Functional differences such as minor population in tumour, self-renewing, proliferation rate, invasion, metastases forming and relapses, activation of neoangiogenesis, resistance to systemic therapy, responsible for tumour heterogeneity, hierarchical organization of tumour tissue, environmental influences and random processes [4,5].

Some molecules such as CD133, CD44, ABCG2, ALDH are known as the biomarkers of some kind of cancer stem cells [6].

During carcinogenesis any cell type is lead to malignant transformation depends on the degree of accumulation of nononcogenic or oncogenic mutations [4]. MicroRNAs regulate gene expression during post transcriptional level. Signaling pathway networks plays an important role in CSCs to keep stem cell properties [7].

The progresses of understanding of the molecular basis of cancer stem cells, involved into the progress in cancer detection and treatment [8]. Many advanced cancers are returned because of the use of chemotherapeutic and radiotherapeutic agents that known as conventional therapies are initially lead to therapeutic responses. They have a less ability to target cancer stem cells and toxicity due to non-specific effects on normal cells. Identification of surface

markers and their molecular features which associated with CSC phenotype may help with the design of effective treatments recently [9]. Other main current therapies are surgery, hormonal therapy, anti-angiogenesis therapy, and immunotherapy. They show a lack of efficacy to long-term outcome. These therapies are mediating with microenvironment signals, inhibiting of drug-efflux pumps, miRNA expression, induction of CSCs apoptosis and differentiation. Current therapies also fail to consider the heterogeneous nature of tumors and the differences in tumors between patients, instead applying broad treatment principles rather than personalized treatment regimens.

Recently, several natural compounds were found which have the ability to kill cancer stem cells, such as salinomycin, curcumin, sulforaphane, vitamin D3 analog and so on [10]. The more recent developments of CSC research are undergoing on carcinomas that are able to undergo an EMT (epithelial-to-mesenchymal transition) program which targets the metastasis and drug resistance ability of CSCs [11]. Therapeutics that based on CSCs has been developed and some are on under research now. The natural compounds which can target the cancer stem cells, the mesenchymal stem cells may able to induce cell differentiation in tumor bulk and some other therapies including gene therapy.

Current researches and their study of cancer stem cells will help to develop recent therapies to eliminate cancer and the initiating cancer stem cells.

CANCER STEM CELLS AND THEIR CHARACTERISTICS

Stem cells are defined as undifferentiated cells that have an ability of self-renewing and differentiating into a large number of diverse mature progeny [12]. Also, Recent studies have suggested that CSCs are tumor-initiating cells that can self-renew and have pluripotent capacity [1].

Stem cells are rare in most tissues. Cause of stem cells must be identified and purified carefully from a tissue-specific stem cell, according to study their properties [2]. Cancers of the hematopoietic system (leukemia) provide the best evidence on normal stem cells are the targets of transforming mutations, and that cancer cell proliferation is driven by cancer stem cells. HSCs are the best studied somatic stem cells have been isolated from mice and humans which have been shown to be responsible for the generation and regeneration of the hematolymphoid systems. Stem cells from a variety of organs have the potential to be used for therapies. HSCs are the main component in bone-marrow transplantation that has already

been used in therapies extensively. Purified HSCs can form the non-hematopoietic tissues that have a greater differentiation potential.

The cancer stem cells have many properties of the normal stem cell Such as long lifespan cause of relative quiescence, resistance to drugs and toxins, and resistance to apoptosis [13].

CSCs have some main key characteristics.

2.1.Self-renewal

Self-renewal is the process by which stem cells divide to make more stem cells. The CSCs subpopulation can be serially transplanted through multiple generations, indicating the self-renewing capacity.

2.2.Differentiation

Differentiation of pluripotent CSCs can not only form tumorigenic daughter CSCs by symmetrical cell division but also formed bulk populations of non-tumorigenic cells by asymmetrical cell division.

2.3.Tumorigenicity

Tumorigenicity is the ability of cultured cells to give rise to either benign or malignant progressively growing tumours. The small subpopulation of CSCs has tumorigenic potential when transplanted into animals.

2.4.Metastasis and relapse

Metastasis means the spread of cancer cells from the place where they first formed to another part of the body through the blood or lymph system, and form a new tumor in other organs or tissues in the body [14].

2.5.Therapy resistance

A small number of cells in the tumor bulk have a character of the chemo/radiotherapy resistance. CSCs seem to grow aggressively and metastasize easily. Chemotherapeutic agents and radiotherapy mainly eradicate the dividing cells [15].

2.6.Genomic plasticity

CSCs are originated from normal stem cells, progenitor cells or more differentiated cells through undergoes various types of mutations of genes because of their genomic instability plasticity. The genetic and epigenetic plasticity of these cells may result of the combination of mutations [14].

MECHANISM AND THEIR REGULATION

2.7.Genome alteration

Genome alteration is a major cause of growth in cancer cells and an important source of genome alteration is mutation. DNA damage leading to mutations in protein coding genes, abnormal oncogene activation, and loss of activity in suppressor-genes. An aggregation of such mutations can lead to the formation of cancer cells, and possibly to tumor formation [4].

Normal SCs, progenitor cells or differentiated cells can escape from regulation and become CSCs, cancer progenitor cells or poorly regulated differentiated cells. Tumor Initiating Cells (TICs) can be return back to CSCs. But the CSCs are not always the cell of origin of the suitable clones in cancer [16].

Genomic heterogeneity results in genomic instability and increased proliferation rate. Mutated cells undergo natural selection and these cells live longer and give rise to lineage cells. The clones are generated the tumour grows. so tumour mass is heterogeneous as it consists of clonal variants [1].

MicroRNAs regulate gene expression during post transcriptional level. MicroRNAs play major role not only in biological processes, including cell proliferation, differentiation, development, apoptosis, tumor formation, growth, and progression. Some multiple genes can be regulated by a single microRNA and several different microRNAs may have the same target mRNA, Twist1, Snail1, Zeb1, and Zeb2 are some genes that regulated by microRNAs [7].

3.2. Cell markers and surface molecules

Cause of the close relationship between CSCs and tumor initiation, progression, metastasis and drug resistance, the isolation of these cells from the total cancer cell population is

essential for further studies. These characteristics are arranged by CSC cells that express stem cell marker genes, including Oct4, Sox2, Nanog, c-kit (CD 117), ABCG2, and ALDH. The most common method used to detect CSCs is fluorescence-activated cell sorting (FACS) based on cell surface markers or intracellular molecules such as CD133, CD24, and CD44 are typically identified [17].

3.3. ATP-binding cassette

ATP-binding cassette (ABC) transporters are membrane transporters that can pump various recognizable and structurally unrelated small molecules such as cytotoxic drugs, out of cells at the expense of ATP hydrolysis. Normal SCs and CSCs express high levels of ABC transporters. These facts contribute to multidrug resistance (MDR) because of many anti–tumor drugs can pump out and due to low intracellular drug concentrations. This raised levels of ABC transporters let cancer stem cells to resist current cancer therapies.

3.4. Signaling pathways

Dysregulation of signaling pathway networks plays an important role in CSCs to keep stem cell properties. the pathways and elements are involved to the control of self-renewal and differentiation of cancer stem cells and normal stem cells include PI3K, PTEN36, JAK, Wnt/β-catenin, hedgehog, Notch, NF-κB, Bcl-2, and others. Targeting this irregular signaling pathways are important for the formation of CSCs which approach a new action for cancer therapy [18].

Wnt/β-catenin signaling pathway

Wnt/β-catenin signaling pathway plays a key role in the process of proliferation and differentiation of normal stem cells. The abnormal activity of this pathway is pathway is the main cause for these types. The Wnt signaling pathway can inhibited by Wnt inhibitory factors and they affected to Wnt target enzyme cyclooxygenase. A CSC TF (transcription factors) such as Achaete-Scute Homolog 1 (ASCL1) gene is considered as an upstream regulator of the Wnt signalling pathway. ASCL1 activates the Wnt pathway by repressing the negative regulator Dickkopf-related Protein 1 (DKK1) gene in glioblastoma (GBM) CSCs in vivo [19].

3.4.1. Notch signaling pathway

Notch signaling pathway plays an important role in the normal stem cell's proliferation, differentiation, apoptosis, and intercellular communication. It involves in both oncogenic or oncosuppressive in tumorigenesis [14]. Notch signaling pathway is closely involved to the CSCs. The notch-1 overexpression in MCF-7 breast cancer cell line showed that the inhibition of the notch signaling increases the CSC apoptosis rate without affecting the various cancers such as T-cell acute lymphoblastic leukemia, melanoma, breast cancer, meningioma and lung adenocarcinoma [7,19].

3.4.2. Hedgehog signaling pathway

It was first discovered by the Drosophila Melanogaster fly through researches. Hedgehog signaling (Hh signaling) is a classic stem cell regulation pathway which found variety of stem cells during early development of parts of body through embryogenesis. In addition, they also play an important role in self-renewal of stem cells and mainly responsible for treatment resistance of cancer cells. There are three subpathways as the Sonic Hedgehog (SHH) (which mediated to the development of CNS, limbs and skeletal system), the Desert Hedgehog (DHH) (which involved to development of germline cells and Schwann cells) and the Indian Hedgehog (IHH) (which involved in the cartilage differentiation) which involved during embryogenesis [19].

4. THERAPIES

The improved understanding on the molecular mechanisms responsible for CSC therapeutic resistance may provide the useful results for current cancer therapies [8]. Conventional anti-cancer therapies kill the bulk of the heterogeneous tumour mass and resulting in tumour shrinkage [9].

Mainly Chemo and radiotherapies are named as the conventional therapies for cancer because they have an ability that results in treatment failure and cancer recurrence. They may affect also healthy tissues [20]. These therapies are based on the specific properties of cancer stem cells (CSCs) such as self-renewal ability, slow rate of division, high expression of removing cytotoxic elements through drug-efflux pumps and ATP binding cassettes (ABC), high capacity for DNA repairing, and also microenvironment characteristics. Therefore, targeting CSCs became essential in treating cancer and preventing tumor relapse [21].

These therapies mainly target to destroy the CSCs and their niches, targeting specific surface markers, signaling pathways. Also, the traditional therapies mediating with microenvironment signals, inhibiting of drug-efflux pumps, miRNA expression, induction of CSCs apoptosis and differentiation. Some of them are successfully used according to clinical properties which mainly in combination with traditional therapies, and others are still under evaluation [20].

Current therapies also fail to consider the heterogeneous nature of tumors and the differences in tumors between patients, instead applying broad treatment principles rather than personalized treatment regimens [22].

4.1. Chemotherapy

Chemotherapy is one of the standard methods of treatment in many cancers. While chemotherapy is often capable of inducing cell death in tumors and reducing the tumor bulk, many cancer patients experience recurrence and ultimately death because of treatment failure. In recent years, CSCs have achieved to initiate cancer cells that may also play an important role in recurrence by this chemotherapy. For the improved understanding on chemotherapy, there are some mechanisms should study including ABC transporter expression, aldehyde dehydrogenase (ALDH) activity, B-cell lymphoma-2 (BCL2) related chemoresistance, enhanced DNA damage response and activation of key signaling pathways [23].

The identification of new indications for old drugs are obvious. These drugs have long been out of patent protection and their use should, therefore, be much cheaper than for newly developed drugs, which is an important aspect in the current discussion on costs of tumor treatment. In addition, they have already undergone clinical trials, their potential toxicity, side effects, pharmacokinetics, contraindications, and possible drug-drug interactions are known. Tumor stem cell-directed drugs should be able to prolong the efficacy of cytotoxic therapy and reduce recurrence risk. On the other hand, combined administration has significantly greater chances of total elimination of all tumor cells [15].

4.1.1. Targeting drug transporters

Membrane efflux transporters, which are mainly, located in blood-brain barrier, hepatocytes, intestinal cells or kidney proximal tubules. They play important roles by interfering with drugs normal functions such as metabolism, availability, and toxicity in human body. Various

researches proved that transporter-mediated drug plays an important role in mediating chemoresistance of cancer cells and CSCs. There are main efflux transporters such as the ATP-binding cassette (ABC) transporters (includes ABCB1, ABCG2 mainly and also ABCB5) [24].

ABCB1 are known to be expressed in the majority of drug resistant tumours which produce the multidrug resistance (MDR1) gene. It acts as an ATP-dependent efflux pump to various anti-cancer drugs. High expression of ABCB1 would lead to the development of chemo-resistant cells. ABCG2 has a high capacity to transport different substrates in chemotherapeutic drugs. Higher ABCG2 expression can found in different CSCs with co express of CD133 and it up regulated by hypoxia through hypoxia-inducible transcription factor complexes (HIF-1α and HIF-2α) [15].

4.1.2. Targeting the tumour microenvironment

The heterogeneous tumor microenvironment (cancer cell-niche) provides different self-protection mechanisms which empower a dynamic interaction with surrounding cells including immune cells. Cytokines and chemokines regulate proliferation, maintenance and self-renewal of CSCs. Less malignant tumors may have more demand on the stem cell-niche but upon cancer progress, this dynamic interplay might be weakened or even diminished. It can escape immune surveillance. CSC microenvironment stimulates the host antitumor responses. Productions of prostaglandin E2 (PGE2) by tumor cells are suppressed immunity and induced inflammation. So, the antagonists of PGE2 receptor has proven successful to block the immuno-suppression and preventing cancer metastases. Also, the CSC niche plays a major role in cancer cell progression and it mostly involves hypoxia, nutrition, and low pH [24].

4.1.3. Role of CSC-related signaling pathways in chemoresistance

The CSCs characteristics depend on various cellular signals, which found in stem cell niche. The most diseases are involved with signaling pathways such as Wnt-β-catenin, Notch and Sonic Hedgehog signaling. Researches under these pathways and their drug inhibitors are invented as the drugs that have an ability to resist CSCs (chemoresistance ability) [15].

WNT/β-catenin signaling pathway, which is required for normal stem and CSC self-renewal in a number of cell types. Chemical activation of the WNT pathway was study by enhanced

renewal of OV6+ hepatic CSCs. These OV6+ hepatic CSCs express the chemoresistance to cisplatin by knockdown the lentiviral microRNA to β-catenin. WNT/β-catenin signaling pathway can also confer chemoresistance to 5-FU and Dox [23].

Inhibition of Wnt/β-catenin signalling pathway by siRNA or by small molecule XAV939 was reported to induce cell death in several types of cancer cells [19]. High Wnt pathway activity marks colon or leukemia CSCs and is required for stemness signature as a prognostic marker [15].

Notch signaling pathway is a pathway which plays an important role in CSC maintenance and chemoresistance. In some cancers such as colon cancers, oxaliplatin used as a treatment which induced Notch activation. siRNA have an ability to knockdown Notch 1 or γ-secretase inhibitor (GIS) treatment which inhibit Notch pathway activation within chemoresistance. Notch pathway may combine with another signal pathways to the purpose of chemoresistance in CD133+ glioma CSCs. Abnormal activation of the SHH pathway was reported in a number of CSC models [19].

Disulfiram is an inhibitor of aldehyde dehydrogenase for the treatment of alcoholism but it is a substance of the self-protection of the CSCs. It used for the clearance of CSCs. Thioridazine is an inhibitor of dopamine receptors which use in tumor therapies based on CSCs in several types of tumors. Niclosamide is known as an antiparasitic and inhibitor of oxidative phosphorylation which mediated with various signaling pathways such as Wnt-β-catenin, Notch, PI3'K-Akt - mTOR, STAT-3 and NFκB signaling pathways [15].

4.1.4. Manipulation of miRNA expression

MicroRNAs (miRNAs) are long non-coding RNAs that regulate self-renewal, differentiation, and division of cells via post-transcriptional gene silencing. miRNAs can act as both tumor suppressors and oncogenes, both of which are deregulated in cancers.

For example, microRNA-34a (miR-34a) is a direct target of tumor suppressor gene p53 and down-regulated in many cancers. It is a tumor suppressor that acts by targeting multiple oncogenes such as c-Met, Notch-1, Notch-2 and CDK6 that inducing the differentiation of CSCs. MiR-21 and miR-205 are highly expressed and predicted to act as oncogenes by targeting the tumor suppressor genes in head and neck cancer cell lines [14].

4.1.5. Ionophore antibiotics

They are produced to selectively kill cancer stem cells and to overcome multidrug resistance. But the significance of drug transporters for treatment with these compounds are lacking. Ionophore antibiotics such as salinomycin and nigericin were ineffective against ovarian cancer cells (including either ABCB1 or ABCG2) which expressed high levels of ABC drug transporters [38].

4.2. Radiotherapy

Radiotherapy is a one of main conventional treatment for cancer and different types of tomors have an ability to recur after this therapy. Each radiotherapy may vary according to the patients' availability such as clinical predictors, tumor stage, histology and performance status. CSSs are the minor subpopulation of tumor bulk which response to therapies.so the therapies directly target the CSCs to completely prevent the tumor bulk [11].

The radiation dose which use to eradicate a tumor and a number of CSCs in the tumor has a combination. As an example, the same radiation dose with a tumor in lower number of CSCs show higher control rate compared with a tumor of higher numbers of CSCs cause of the tumor volume and density depends on the radiation dose [25]. Because of the constant plasticity of CSCs, number of CSCs contained in a tumor and the radiation dose necessary to permanently cure 50% of the tumors (tumor control dose 50%, TCD50) [26].

Radiotherapies targeting CSCs by using their radioresistance ability, pathways of self-renewal, the CSC microenvironment and several signal pathways such as wnt and notch pathways, Cell cycle, DNA repair, ROS mechanisms, apoptosis and autophagy pathways are associated with CSCs in radioresistance [11].

Recent researchers have identified several new therapies such as carbon ion radiotherapy and internal radiotherapy with copper-64-diacetyl-bis (N4-methythiosemicarbazone) (64Cu-ATSM) used to target CSCs [11].

4.2.1. DNA damage repair

The effects of irradiation process lead to cell death cause by the activation of the DNA damage response (DDR) mechanisms. The various types of DNA damages occur as the result of the ionizing irradiation such as single strand breaks (SSBs), double strand breaks (DSBs),

damaged nucleotide bases. DSBs represent the major lesions which lead to cell death. Both normal and cancer cells can repair DSBs by either error-free homology-directed recombination (HR) or error-prone non-homologous end joining (NHEJ) mechanisms. DNA damage induces checkpoint kinase signaling pathways such as ataxia telangiectasia mutated (ATM)-checkpoint kinase 2 (Chk2) and ATM-Rad3-related (ATR)-checkpoint kinase (Chk1) which inhibit cell cycle progression in order to activation of DNA repair process. The activation of cell cycle chk1 and chk2 was found in CD133 marker cells [26,27].

4.2.2. Targeting CSC niche

Another kind of treatment is targeting to the supportive environment for CSCs.it called as CSC niche or microenvironment. Modification of the tumor microenvironment appears to be a potential therapy for eradicating the growth of CSCs. Targeting CSCs with their niche appears to be a way for future research in combing specific drugs with radiation [11].

4.2.3. Hypoxia, ROS and Apoptosis

Oxygen is a one of the most effective radiosensitizing agents. Tumors contain areas of low oxygen cells in these areas are considered as protected from radiation. Tumor hypoxia cause to improve radiation treatment results. The efficiency of anti-angiogenic therapies combined with radiation and they may target the CSC microenvironment than tumor cells in general. Anti-angiogenesis combined with radiation supports the importance killing CSCs over the normal cells in the tumor bulk [28].

ROS (reactive oxygen species) is one of the most important regulatory mechanisms for CSCs. The lower levels of ROS in subpopulation of CSCs in some tumors compared to non-CSCs populations, resulted to increase the levels of free-radicals which contribute to the tumor radioresistance. Indication of the ROS level is combined with CSC and radioresistance [27].

Apoptosis is an essential factor in CSCs after radiation. The CD133+ Huh-7 liver CSCs have a greater anti-apoptotic activity through increased Bcl-2 expression and radioresistance. The CD133+ thyroid cancer cells also showed higher anti-apoptotic rate after radiation. The role of autophagy as an alternative cell death mechanism Autophagy was believed as a non-apoptotic programme of cell death or cell death to distinguish from apoptosis. In cancer therapy, the role of autophagy is still doubtful but this cellular process may serve as a pro-survival or pro-death mechanism to counteract or mediate the cytotoxic effect of anticancer

agents. There is only a little evidence for the role of autophagy in CSC-associated radioresistance. It was found that radiosensitivity of glioma stem cells can be increased by inhibiting autophagy-related proteins Becline-1 and ATG5, indicating that the induction of autophagy contributes to radioresistance of glioma stem cells [28].

4.2.4. Signaling pathways in cancer radioresistance

Understanding the signaling pathways may developed the radioresistance for various treatments for patients and enhance the radiosensitivity in human cancers. [29]

The Notch pathway is activated in endothelial cells by IR shifting up-regulation of Jag1 and Hey1 genes. Activation of Notch pathway is giving a combination with poor prognosis and radioresistance in NSCLC patients. The inhibition of Notch pathway with gamma-secretase inhibitors (GSIs) considered that glioma stem cells more sensitive to radiation at clinically suitable doses. The non-adherent anoikis-resistant stem cells such as CaP cells after radiotherapies are showed that the activation of Notch pathway and increased expression of stem cell markers such as CD133, Oct-4, Sox2 and Nanog. The inhibition of Notch pathway may improve the current radiation treatment for cancer [29].

Wnt/β-catenin pathway is also involved in CSC radioresistance. The up-regulation of the Wnt/β-catenin pathway is important for KYSE-150 RR esophageal cancer cells. The downregulation of miR-301a induced radioresistance in esophageal cell line KYSE-150R through the upregulation of Wnt1. The Wnt/β-catenin signal pathway plays a major role in radioresistance. Inhibition of Wnt/β-catenin pathway is radiosensitize the CaP cells through decreasing aldehyde dehydrogenase (ALDH). The radiosensitivity of cancer cells may enhanced by inhibiting the Wnt/β-catenin pathway [29].

4.3. Immunotherapy

The immunotherapy targeting CSCs are recently developed in fast few decades'. These therapies mainly based on the immune system and immune response which involved preventing the tumor growth [34]. The proper understanding on the characteristics of CSCs with immune system and the tumor niche contribute to provide the novel therapies targeting CSCs [30]. Anticancer immunotherapeutic can classified according to antigen specificity. Mainly immunotherapies specifically target one or a few specific tumor-associated antigens [31].

Tumor cells stimulate the immune cells to produce more inflammatory cytokines that induce tumor proliferation, invasion, and angiogenesis. So, the inflammation in the tumor niche contributes to various types of cancer progression such as prostate cancers. These observations may mediate to modulate the immune response into an effective antitumor therapy [32].

4.3.1. Targeting immune checkpoints

The most advanced activating therapeutic antitumor immunity is inhibition of immune checkpoints which can maintain the self-tolerance by targeting T cells and tumor antigens [33]. Lots of immune checkpoints are originated by ligand–receptor interactions that can blocked by antibodies or recombinant forms of ligands or receptors. There are different drugs targeting immune check-points such as cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed cell death/ligand-1 (PD-1/PD-L1) [39]. CTLA4 antibodies were the first of this class of immunotherapeutics which achieve US Food and Drug Administration (FDA) approval. PD1 enhance the antitumour immunity. These drugs do not affect against the tumor or they are not effective for loner period in lot of cases because of the lack expression of human leukocyte antigens [34]. They can involve future approaches to immuno-oncology combination therapy [35].

4.3.2. Treatment vaccines

CSCs by low express of MHC-I and over expressing of IL-4 are evaded from cytotoxic T lymphocytes. Boosting T-cell response can used to eradicate CSCs. It can achieve by boosting neo-antigens within CSCs and it considered as tumor vaccination [15].

Some immune therapies boost the T-effector cell response. As an example the PROSTVAC-F(PSA) vaccine consists main components such as vaccinia virus expressing PSA transgene for the first immunization, PSA fowlpox vector expressing PSA transgene used for reduce the development of neutralizing antibody responses and a viral vector encoding three major molecules (B-lymphocyte activation antigen B7-1 , intercellular adhesion molecule 1 (ICAM-1) , and lymphocyte function-associated antigen 3 (LFA-3) which activate lymphocytes during antigen presentation by antigen-presenting cells (APC) [32].

4.3.3. Adoptive cell transfers

It is a treatment that effort to boost the natural ability of T cells to fight cancer. CSC-specific T cells are taken from various tumors and grown in vivo by using mice. Also, the genetically modified T cells to express chimeric antigen receptors (CAR T-cells) provide remarkable benefit for patients suffering from different cancers. It called CAR T-cell therapy [32].

4.4 Hormonal therapy

Hormone therapy for cancer is a one of the major treatments targeting cancer cells. It involves the endocrine system through exogenous or external administration of specific hormones such as steroid hormones or hormone antagonists. Steroid hormones are involved to gene expression in certain cancer cells such as breast cancer, prostate cancer, ovarian cancer, endometrial cancer, cancers in adrenal cortex etc. cause of changing the levels or activity of different hormones it can be result to occur cancers. Surgical removal of endocrine organs can be a form of hormonal therapy such as orchiectomy and oophorectomy. But this therapy does not work for all cancer types.

4.4.1. Breast cancer and hormone therapy

The breast cancer stem cells (BCSCs) have an ability of hormone resistance. In breast cancer, both estrogen and progesterone signaling affected the CSCs activity [36]. There are some estrogen receptors (ER) as ERα and ERβ which expresses the breast cancer cell lines contained ER-negative cancer stem cells. as the result, the normal breast cell proliferation process may stimulus and occurs breast cancers. Estrogen indirectly affected with ER-negative CSCs by product the paracrine factors [36].

Anti-estrogen therapies mainly used for breast cancer treatment of ER-positive tumors. The drugs which used as the estrogen receptor modulators as tamoxifen and fulvestrant as well as aromatase inhibitors reduce estrogen synthesis. Hormone therapy by using tamoxifen or raloxifene might be helped to people at high risk of breast cancer.

4.4.2. Prostate cancer and hormone therapy

Hormone therapy inhibits the amount of testosterone in the body. The pituitary gland produces luteinising hormone (LH) and it regulate the amount of testosterone in testicles. LH blockers inhibit the production of LH. They block the signal pathway from the pituitary gland

to the testicles. LH blockers such as goserelin (Zoladex), leuprorelin (Prostap) and triptorelin (Decapetyl) used to treat the prostate cancers. Also, there is Gonadotrophin releasing hormone (GnRH) blockers which inhibit the messages from hypothalamus to produce LH by pituitary gland to produce more testosterone from testicles. The drug called degarelix (Firmagon) is used as a GnRH blocker.

4.4. Anti-Angiogenesis therapy

Cancer has the ability of metastasis which spread to adjacent or distant organs through circulating the intravascular system within blood or lymphatic vessels and proliferate at another place. Angiogenesis and lymphangiogenic are the processes where the new blood and lymphatic vesicles are formed. It has a major role to form new vascular network to supply nutrients, oxygen and immune cells, and to remove unwanted products [37].

Angiogenesis is regulated by both stimulator and inhibitor molecules. Angiogenesis signals express some genes in the host tissue to produce proteins which stimulate the growth of blood vessels. The angiogenic inhibitors reduce the mortality and morbidity of CSCs. There are five classes of angiogenic inhibitors as inhibitors of proteases, endothelial cell migration and proliferation, angiogenic growth factors, matrix proteins on the endothelial cell surface and inhibitors with unique mechanisms. antiangiogenic drugs used combine with chemotherapy or radiation therapy. Cytotoxic agents and antiangiogenic agents have an ability to destroy cancer cells and endothelial cells through higher levels of vascular endothelial growth factors (VEGF). The new formed vesicles are structurally and functionally abnormal. Also, the blood vessels are immature and leaky. So, the pressure generated from proliferating cancer cells by contracting blood and lymphatic vessels in tumor and provides an abnormal niche through reducing the blood supply, interstitial hypertension and hypoxia. For this process, low-dose anti-VEGF can use as a treatment [37,8].

5. DISCUSSION

CSCs are the cells that initiate tumors and derived from normal stem cells, progenitor cells and mature differentiated cells. And they contribute to tumor resistance on treatments. They have some key characteristics such as self-renewal, tumorigenicity, metastasis, differentiated, drug resistance etc. there are lots of mechanisms and regulatory pathways are involved to CSCs like ABC transporters, signaling pathways and genome alterations. The proper understanding of the molecular basis of CSCs may involve to invent lot of therapies for

cancer. Mainly chemotherapy and radiotherapy are known as conventional therapies and there are more other therapies like immune therapy, hormonal therapy, anti-angiogenic therapies. There are more treatments still undergoing the clinical trials.

ACKNOWLEDGEMENTS

International College of Business and Technology (ICBT) No. 36, De Kretser Place, Bambalapitiya, Colombo 04, Sri Lanka and the Department of Biomedical Science at ICBT is gratefully acknowledged for all the Support and Encouragement.

REFERENCES

1. Fulawka, L., 2014. Cancer stem cells - the current status of an old concept: literature review and clinical approaches. Biol Res, 47(1), p. 66.
2. Reya, T. S. J., 2001. Stem cells, cancer, and cancer stem cells. Nature, 414(6859), pp. 105-11.
3. Botelho, M., 2016. Significance of Cancer Stem Cells in Anti-Cancer Therapies.. International Journal of Immunotherapy and Cancer Research, 2(1), pp. 14-16.
4. Hsu, Chueh Lin, 2016. Genotypes of cancer stem cells characterized by epithelial-to-mesenchymal transition and proliferation related functions. Scientific Reports, 6.
5. Sampieri K1, F. R., 2012. Cancer stem cells and metastasis. - PubMed - NCBI. Semin Cancer Biol., 22(3), pp. 187-93.
6. Hu, Y., 2012. Targeting cancer stem cells: a new therapy to cure cancer patients. American journal of cancer research, 2(3), pp. 340-56.
7. Wang, Zhen, 2016. The molecular mechanism and regulatory pathways of cancer stem cells. Cancer Translational Medicine, 2(5), p. 147.
8. Eyler, Christine E, 2008. Survival of the fittest: cancer stem cells in therapeutic resistance and angiogenesis. Eyler, Christine E-Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 26(17), pp. 2839-45.
9. Deshmukh, Abhijeet, 2016. Cancer stem cell metabolism: A potential target for cancer therapy. Molecular Cancer, 15(1).
10. Taylor, Wesley F., 2017. The use of natural products to target cancer stem cells. American Journal of Cancer Research, 7(7), pp. 1588-1605.
11. Ogawa, K, 2013. Radiotherapy targeting cancer stem cells: current views and future perspectives. Anticancer Res, 33(3), pp. 747-754.
12. Guo, W. E. I., 2006. Cancer stem cells. Pediatric research, 59(4 Pt 2), pp. 59R-64R.
13. Cells, S.-l. C., 2009. Forum Review Article Redox Regulation and Its Emerging Roles in Stem Cells and Stem-Like Cancer Cells. Antioxid Redox Signal, 11(5), pp. 1107-1122.
14. Han, L., 2013. Cancer stem cells: therapeutic implications and perspectives in cancer therapy. Acta Pharmaceutica Sinica B, 3(2), pp. 65-75.
15. Pattabiraman, D. R., 2014. Tackling the cancer stem cells — what challenges do they pose?. Nature Reviews Drug Discovery, 13(7), pp. 497-512.
16. Aponte, P. M., 2017. Stemness in cancer: Stem cells, cancer stem cells, and their microenvironment. Stem Cells International, Volume 2017.
17. Dawood, S., 2014. Cancer stem cells: implications for cancer therapy. Oncology (Williston Park, N.Y.), 28(12), pp. 1101-1107.
18. Chen, K., 2013. Understanding and targeting cancer stem cells: therapeutic implications and challenges. Acta Pharmacologica Sinica, 34(6), pp. 732-740.
19. Ciurea, M. E., 2014. Cancer stem cells: biological functions and therapeutically targeting.. International journal of molecular sciences, 15(5), pp. 8169-85.

20. Dragu, D. L., 2015. Therapies targeting cancer stem cells: Current trends and future challenges. World journal of stem cells, 7(9), pp. 1185-201.
21. Insan, M. B., 2014. New approaches to target cancer stem cells: current scenario. Mini reviews in medicinal chemistry, 14(1), pp. 20-34.
22. Ebben, J. D., 2010. The cancer stem cell paradigm: a new understanding of tumor development and treatment. Expert Opinion on Therapeutic Targets, 14(6), pp. 621-632.
23. Abdullah, L. N., 2013. Mechanisms of chemoresistance in cancer stem cells. *Clinical and Translational Medicine*, 2(1), p. 3.
24. Aponte, P. M., 2017. Stemness in cancer: Stem cells, cancer stem cells, and their microenvironment. *Stem Cells International*, Volume 2017.
25. Boesch, M., 2015. Drug Transporter-Mediated Protection of Cancer Stem Cells From Ionophore Antibiotics. *STEM CELLS Translational Medicine*, 4(9), pp. 1028-1032.
26. Botelho, M., 2016. Significance of Cancer Stem Cells in Anti-Cancer Therapies.. *International journal of immunotherapy and cancer research*, 2(1), pp. 14-16.
27. Cells, S.-l. C., 2009. Forum Review Article Redox Regulation and Its Emerging Roles in Stem Cells and Stem-Like Cancer Cells. *Antioxid Redox Signal*, 11(5), pp. 1107-1122.
28. Chang, L., 2016. Cancer stem cells and signaling pathways in radioresistance.. *Oncotarget*, 7(10), pp. 11002-17.
29. Chen, K., 2013. Understanding and targeting cancer stem cells: therapeutic implications and challenges. *Acta Pharmacologica Sinica*, 34(6), pp. 732-740.
30. Ciurea, M. E., 2014. Cancer stem cells: biological functions and therapeutically targeting.. *International journal of molecular sciences*, 15(5), pp. 8169-85.
31. Dawood, S., 2014. Cancer stem cells: implications for cancer therapy.. *Oncology (Williston Park, N.Y.)*, 28(12), pp. 1101-1107,1110.
32. Dayyani, F., 2011. Novel therapies for metastatic castrate-resistant prostate cancer. *Journal of the National Cancer Institute*, 103(22), pp. 1665-1675.
33. Deshmukh, Abhijeet, 2016. Cancer stem cell metabolism: A potential target for cancer therapy. *Molecular Cancer*, 15(1).
34. Deshmukh, A., 2016. Cancer stem cell metabolism: A potential target for cancer therapy. *Molecular Cancer*, 15(1).
35. Dragu, D. L., 2015. Therapies targeting cancer stem cells: Current trends and future challenges.. *World journal of stem cells*, 7(9), pp. 1185-201.
36. Ebben, J. D., 2010. The cancer stem cell paradigm: a new understanding of tumor development and treatment. *Expert Opinion on Therapeutic Targets*, 14(6), pp. 621-632.
37. Eyler, Christine E, 2008. Survival of the fittest: cancer stem cells in therapeutic resistance and angiogenesis. *Eyler, Christine E-Journal of clinical oncology: official journal of the American Society of Clinical Oncology*, 26(17), pp. 2839-45.
38. Eyler, C. E., 2008. Survival of the fittest: cancer stem cells in therapeutic resistance and angiogenesis. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*, 26(17), pp. 2839-45.
39. Fulawka, L., 2014. Cancer stem cells - the current status of an old concept: literature review and clinical approaches. *Biol Res*, 47(1), p. 66.
40. Fulawka, L., 2014. Cancer stem cells - the current status of an old concept: literature review and clinical approaches. *Biol Res*, 47(1), p. 66.
41. Galluzzi, L., 2014. Classification of current anticancer immunotherapies. *Oncotarget*, 5(24), pp. 12472-12508.
42. Gerweck, L. E., 2016. At the crossroads of cancer stem cells, radiation biology, and radiation oncology. *Cancer Research*, 76(5), pp. 994-998.
43. Guo, W. E. I., 2006. Cancer stem cells. *Pediatric research*, 59(4 Pt 2), pp. 59R-64R.
44. Han, L., 2013. Cancer stem cells: therapeutic implications and perspectives in cancer therapy. *Acta Pharmaceutica Sinica B*, 3(2), pp. 65-75.
45. Hsu, Chueh Lin, 2016. Genotypes of cancer stem cells characterized by epithelial-to-mesenchymal transition and proliferation related functions. *Scientific Reports*, Volume 6.

46. Hu, Y., 2012. Targeting cancer stem cells: a new therapy to cure cancer patients. *American journal of cancer research*, 2(3), pp. 340-56.
47. Insan, M. B., 2014. New approaches to target cancer stem cells: current scenario. *Mini reviews in medicinal chemistry*, 14(1), pp. 20-34.
48. KIM, Y. S., 2013. Low Production of Reactive Oxygen Species and High DNA Repair: Mechanism of Radioresistance of Prostate Cancer Stem Cells. *Anticancer Research*, 33(10), pp. 4469-4474.
49. Krause, M., 2017. Cancer stem cells: Radioresistance, prediction of radiotherapy outcome and specific targets for combined treatments. *Advanced Drug Delivery Reviews*, Volume 109, pp. 63-73.
50. Maccalli, C., 2017. Immunomodulating and Immunoresistance Properties of Cancer-Initiating Cells: Implications for the Clinical Success of Immunotherapy. *Immunological Investigations*, 46(3), pp. 221-238.
51. Melero, I., 2015. Evolving synergistic combinations of targeted immunotherapies to combat cancer. *Nature Reviews Cancer*, 15(8), pp. 457-472.
52. Nishida, N., 2006. Angiogenesis in cancer. *Vascular Health and Risk Management*, 3(2), pp. 213-219.
53. Ogawa, K, 2013. Radiotherapy targeting cancer stem cells: current views and future perspectives. *Anticancer Res*, 33(3), pp. 747-754.
54. Papaccio, F., 2017. Concise Review: Cancer Cells, Cancer Stem Cells, and Mesenchymal Stem Cells: Influence in Cancer Development. *Stem Cells Translational Medicine*, 6(12), pp. 2115-2125.
55. Pardoll, D. M., 2012. The blockade of immune checkpoints in cancer immunotherapy. *Nature Reviews Cancer*, 12(4), pp. 252-264.
56. Pattabiraman, D. R., 2014. Tackling the cancer stem cells — what challenges do they pose?. *Nature Reviews Drug Discovery*, 13(7), pp. 497-512.
57. Pattabiraman, D. R., 2014. Tackling the cancer stem cells — what challenges do they pose?. *Nature Reviews Drug Discovery*, 13(7), pp. 497-512.
58. Reya, T., 2001. Stem cells, cancer, and cancer stem cells. *Nature.*
59. Reya, T. S. J., 2001. Stem cells, cancer, and cancer stem cells. *Nature*, 414(6859), pp. 105-11.
60. Sampieri K1, F. R., 2012. Cancer stem cells and metastasis. - PubMed - NCBI. *Semin Cancer Biol.*, Volume 22(3), pp. 187-93.
61. Simões, B. M., 2015. The role of steroid hormones in breast cancer stem cells. *Endocrine-Related Cancer*, 22(6), pp. T177-T186.
62. Smyth, M. J., 2016. Combination cancer immunotherapies tailored to the tumour microenvironment. *Nature Reviews Clinical Oncology*, 13(3), pp. 143-158.
63. Taylor, Wesley F., 2017. The use of natural products to target cancer stem cells. *American Journal of Cancer Research*, 7(7), pp. 1588-1605.
64. Vlashi, E., 2009. Radiation responses of cancer stem cells. *Journal of Cellular Biochemistry*, 108(2), pp. 339-342.
65. Wang, Zhen, 2016. The molecular mechanism and regulatory pathways of cancer stem cells. *Cancer Translational Medicine*, 2(5), p. 147.