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Review Article

Cancer Stem Cells and Drug Resistance

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Abstract

Cancer has been the major cause of morbidity and mortality all over the world. Even though cancer therapy has new ways of treatment by chemotherapy and radiotherapy, resistance to treatment has become the major cause for mortality of patients. It has lead to decrease in lifespan of patients even after treatment.

The present review deals with Stem cells (SC), Cancer stem cells (CSC),Epithelial Mesenchymal Transition (EMT)and various aspects of cells leading to drug resistance. The characteristics of CSC like Dormancy, surrounding aspects of tumor like Hypoxia, Tumor microenvironment and Cancer Nische act on the tumor cells in various ways leading to Drug resistance.

Understanding of these various aspects helps in dealing with cancer drug resistance, its effects and various ways to improve tumor response and treatment.

Keywords: Cancer Stem Cell;Epithelial Mesenchymal Transition; Tumor Microenvironment; Drug Resistance

Abbreviations

SC: Stem cells;CSC: Cancer Stem Cells; EMT: Epithelial Mesenchymal Transition

Introduction

Cancer from any site organ, the tissue is known to cause morbidity and mortality worldwide with about 20% of deaths or one-third of affected persons dying of cancer every year [1]. Even though major advances in diagnosis, treatment options are being used many times there is treatment failure due to resistance to drug treatment with recurrence and metastasis.

Metastasis remains the main cause of more than 90% cancer-related deaths as the treatment involves surgery which removes the major part of the tumor with fellow-up by radiotherapy and chemotherapy for the residual tumor [2].

It has been found that chemotherapy induces tumor heterogeneity, the cells being derived from both normal and cancer cells which leads to decreased response to drug treatment [3].

Also, metastasis which is a major characteristic of and malignancy remains the cause for more than 90% of cancer-related deaths [2]. Resistance and metastasis lead to reduce response or increased resistance to therapy. This is seen to be due to tumors of initiating cells or cancer stem cells (CSC). Which are small subpopulations of cells within a tumor that retain the capacity for self-renewal and are a small subpopulation of cells within a tumor that retain the capacity for self-renewal? [2].

They are capable of differentiation into heterogeneous lineages within any tumor. These cells process capacity to grow with resistance to radiation and chemotherapy leading to reoccurrence after treatment[4].

Also, they have localized in a specific microenvironment referred to as a niche. These niches are formed by a variety of cells that promote CSC survival and promote the re-growth or proliferation of these cells. Thus, it is important to understand the importance and features of CSC so as to improvise in the management and treatment of cancer.

Origin of cancer stem cells (CSC)

The origin of cancer stem cells (CSCs) also known as tumor-initiating cells (TICS) have been studied extensively nowadays. The origin of these cells, cellular markers so as to identify this cell, their mechanism of working, so that methods are developed to target their pathways is being studied [5](Figure 1).

CSC was first identified by Bonnet and Dick in 1997 by the identification of a subpopulation of Leukemic cells. Also, they were isolated in vitro in 2002 by the cells isolated from human brain gliomas [6].

The other sites where the CSC population was also identified from several other solid cancers include melanoma, the tumor of the brain, lung, liver, pancreas, colon, breast cancer ovarian cancer [7].

The postulated origin for, CSCs is not clear but observations or hypothesis put forth suggest that depending on the tumor type, CSC might be from adult stem cells, adult progenitor cells, that have undergone mutation or differentiated cancer cells that have obtained stem cells like properties through dedifferentiation [8].

Figure 1: Origin of cancer stem cells CSC.

CSC has plasticity to such extent that not only they are tissue-specific stem cells but also other tissue stem cells are produced by the CSC cells [9].

The other characteristics of CSCs are that they can are generated by dedifferentiation from progenitor cells or differentiated cells these cells are produced when the progenitor cells undergo mutation [10]. There are many examples wherein CSCs cells can be produced like bone narrow cells in CML, neurons can get dedifferentiated into progenitor cells and lead to induction of gliomas [11].

The identification CSCs can be done these are specific markers of manual stem cells that are commonly used for isolating CSCs from solid tumors and other malignancies [12].

All surface markers differ in each cancer type depending on their characteristics and phenotypes. e.g. of cell surface markers are CD133, CD24, intracellular proteins such as a common protein seen in many cancers such as leukemia, breast, a colon is aldehyde dehydrogenase 1(ALDH1).

The surface markers can be used to identify and isolate the CSCs of each cancer type [13].

The various mechanisms by which CSCs lead to regrowth of tumor, resistance to chemotherapy and lead to death, are to be identified and understood. This reason being this helps in adding other supportive measures, to reduce cancer resistance and prolong the survival of patients post-treatment.

The factors or mechanisms involved in CSCs contributing to chemoresistance.

The various ways explained are including:

- Epithelial mesenchymal transition(EMT)
- Intrinsic multidrug resistance (MDR)
- Dormancy of CSCs
- Microenvironment
- Hypoxia
- Presence of immune cells.
- Cancer niche.

Epithelial mesenchymal transition (EMT)

Epithelial to Mesenchymal transition is seen during embryonic development. These states vary from all stable epithelial state through intermediate transition states to a mesenchymal state. This is a highly plastic dynamic state seen in cells. This shift from one state to another is referred to as epithelial to mesenchymal shift (EMT).

The reverse of this is also possible called Mesenchymal to epithelial shift (MET) (Figure 2).

Figure 2: Epithelial mesenchymal transition.

EMT is a process wherein the epithelial cells lose their adhesion capacity loosen and transform to spindle cells that adopt a migratory and invasive behavior.

MET is the reverse of the above process wherein cells lose their migratory freedom adapting back to an apico-basal polarization and expressing, the junctional complexes which are the hallmarks of epithelial tissues [14].

The EMT is formed when there are many signaling factors that stimulate the cells to express specific transcription factors (TFS), called EMT-FTs e.g. Snail Zeb, Twist.

Also, miRNA in the cells is stimulated along with epigenetic and post-translational regulators. All these are involved in various stages of embryonic development, wound healing, fibrosis and above all metastasis of cancer cells.

EMT has found to have many characters that lead to cancer resistance to treatment. The most important is potential for dissociation migration and dissemination to distant sites [15].

The other way EMT can cause chemo resistance is by producing cancer stem cells (CSCs). Stem cells (SC) are essential from the maintenance of tissue homeostasis within multicellular organisms. The main features of SC are by cell division bringing about self-renewal by producing daughter cells which further retain the capacity for self-renewal. The presence of stem cells (SC) in any tissue is important to produce the components of the tissue. Cancer stem cells are cancer cells that they store the capacity of long-term self-renewal with SCs (CSCs)[16].

EMT activates **Sc** signaling pathways inducing CSC characteristics that lead to increased drug resistance e.g. is in head and neck squamous cell carcinoma, EMT affects Hedgehog signaling to lead to acquired types of drug resistance [17].

Another characteristic of cells that undergo EMT is they may stop dividing, thus the tumor will develop resistance drugs which target dividing tumors [18].

Another mode by which EMT plays a role in cancer spread is its role in the production of circulating tumor cells (CTCs) which express both epithelial and mesenchymal markers [19].

EMT also plays a role in metastasis and it is the driver of cancer progression by the cooperation between multiple EMT-TPS leading to loss of adhesion of epithelial cells, invasion, and dissemination of tumor [20].

Another mode by which EMT works is it prevents cell death induced by various means both in embryos and in cancer cells leading to chemoresistance[21](Figure 3).

Figure 3: EMT and cancer drug resistance.

Multidrug resistance (MDR)

Drug resistance in cancer due to various factors had lead to the major cause of death of cancer patients [22]. The modes of drug resistance are many mainly coming under the categories of intrinsic or acquired resistance. Both occur in about 50% of cancer patients with resistance. Intrinsic is the inherent resistance that exists much before the drug treatment while acquired resistance is induced after therapy [23].

Intrinsic drug resistance is defined as the innate resistance to drugs thus reducing the efficacy of the anti-cancer drug treatment. The main routes of resistance are:

- The inherent genetic mutation in the genes involved in cancer cell growth and/apoptosis which leads to EMT thus making the CSCs resistant to more drug therapy.
- Another intrinsic characteristic in cancer cells is their heterogeneity. These are a group of cells in the tumor which are Insensitive including CSCs which will remain as residual tumor even after treatment, leading to relapse in later stages. Therefore the need is to combine the targeting of both CSCs and tumor cells to reduce drug resistance [24].
- Therapeutic effects of drugs or cells can be altered or reduced by activation of intrinsic pathways that act on external agents, which includes environmental toxins including anticancer drugs. eg are protective mechanisms of ATP binding cassette transporter (ABC) medicated drug effective working to reduce cellular drug accumulation.

Acquired resistance

This is seen when resistance to drugs slowly occurs in patients once a period of treatment duration.

The method can be seen either by:

- Activation of a second proto-oncogene to become an oncogene.
- Changes or mutations in the target cells of drugs.
- Changes in the surrounding of tumor cells called tumor micro-Environment (TME) after drug treatment.

Tumour responds initially and regresses in size. Once there is a mutation in the cancer cells there will be regrowth of the tumor [25]. The mutations in genes encoding target proteins will cause a decreased response to drugs targeting the cells.

TME can affect the course of treatment. The mode is the crosstalk between the tumor cells and the microenvironment by the release of exosomes released by cancer cells and stromal cells. The exosomes carry certain miRNAs which are used in the TME environment to communicate with each other loading to drug resistance [26].

Mechanisms of drug resistance are many. The intrinsic and acquired resistance can co-exists during cancer tumor progression and treatment. The importance is one has to do the genomic and biochemical analysis to prolong the effective treatment plans. Thus, the best drug regimen is which prevents or delays resistance (Figure 4).

Figure 4: Causes of multi drug resistance.

Dormancy in cancer

Dormancy of cancer cells is a new concept in cancer re-occurrence after many years of therapy. It is defined as the arrest of tumor growth in the primary site or metastatic focus [27].

In tumor mass dormancy, there is a balance between tumor growth and tumor cell death. This is controlled by mechanisms of antigenic dormancy and immune-mediated dormancy. Cellular dormancy is another mode of dormancy which is characterized by three features of:

- Minimal proliferation
- Minimum death
- Reversibility of cancer cells.

It is seen in cancer stem cells CSCs and tissue stem cells. They are mainly important as they play a role in late recurrence and metastasis wherein the microenvironment plays an important role at the metastatic sites [28].

Importance of dormancy it that it depends on many factors like the cell type, nutrient levels, hypoxia growth factors, microenvironment at metastatic sites which affect the dormancy in various cancer cells (Figure 5).

Figure 5: Dormancy of tumor cells.

The mode of management various as methods of tracking these cells with drugs that target and prevent reoccurrence along with regular treatment, for cancer can improve the treatment of cancer, improve prognosis and prevent a recurrence [29].

Tumor microenvironment

The tumor microenvironment is the cellular environment in which the tumor exists in the human system which includes blood vessels, fibroblast cells that contribute to the immunity, and cells of bone marrow origin like inflammatory cells. The tumor and surrounding immune cells in the microenvironment can lead to tumor angiogenesis and induce peripheral immune tolerance.

Also the surrounding non- malignant cells can cause tumor progression, invasion, and metastases [30]. The tumor microenvironment can be used for diagnosis and therapy of cancer.

Thus the newer treatment methods of common cancers of organs like breast, lung, and pancreas can be effectively done by targeting also the microenvironment like stromal cells, blood vessels, collagen which plays a role in tumor growth and metastasis [31].

Thus, by evaluating the microenvironment using molecular and cellular profiles, it is easier & important to identify the elements of the microenvironment, to improve cancer response by targeting the microenvironment along with tumor therapy to kill cancer cells.

Hypoxia

Hypoxia of tissue is a pivotal factor in the development of angiogenesis development maintenance of self-renewal characterizes of CSC which are known to be located near hypoxic zones of tumors [32].

The main cellular response to hypoxia is triggered by over expression of hypoxia-inducible factor -1lapha (HIFI-) which at high oxygen levels is ubiquitinated and subsequently degraded. When O_2 levels decrease ubiquitination is inhibited and subsequently degraded which O_2 levels decrease thus is activation HIFI- which enters the nucleus dimerizes with the other factor called hypoxia-inducible factor 1B 9 (HIFB1B). This causes the activation of and transitions of hypoxia response elements leading to stimulation of angiogenesis, activation of the proliferation of CSCs and initiation of survival pathways of cancer cells [33].

The metastasis of tumor cells occurs by the induction of angiogenesis due to hypoxia. It also happens by the formation of Hypoxia-induced EMT wherein there is a decrease in Epithelial associated gene expression such as E-cadherin, β-catenin and an increase in mesenchymal-like gene expression such as N cad, vimentin, SMA and CxCR4 which increase the plasticity of the cells leading to invasion and metastasis to a more oxygen available homing site. Resistance to radiation and chemotherapy due to hypoxia is also noted [34].

Since hypoxia confers quiescence with the protection of cells from external stress. It causes a decrease in death or apoptosis of cells with a decrease in P53 activity. Thus, hypoxia also leads to a decrease in drugs reaching and entering cells leading to chemoresistance [35].

Radiation is effective in dividing cells in the G2/M phase where DNA repair mechanisms are the most prone to malfunction. It is not effective on quiescent cells which are seen in hypoxic regions thus leading to radioresistance [35].

Hypoxia can affect the cellular component like stromal cells Extracellular components cytokines and other mediators leading to blood vessel formation and nutrients to tumor cells leading to tumor growth and metastasis [36].

Even hypoxia is noted to affect immune cells leading to immunosuppression this helps the tumor to grow to metastasize as it escapes immune surveillance [37].

Since hypoxia helps tumor growth spread and resistance to treatment this is a need to have methods to,directly and indirectly, measure hypoxia and bring about changes in the treatment of resistant cancers.

Immune cells and cancer therapy

The immune cells present in the microenvironment are macrophages, neutrophils lymphocytes, dendritic cells, natural are killer cells or myeloid-derived suppressor cells.

Macrophages are known to play both antitumor and tumoral activity based on the interleukins which activate them [38]. Their quality of plasticity can be used in cancer therapy.

There are trials wherein macrophages can be activated by various elements like interferon's oncologic views to target or mediate cancer cell killing by chemo drugs.

They can also be carriers in gene therapy or carriers of enzymes activating prodrugs [39]. The other important immune cell the neutrophils known as the first line of defense can be associated with a tumor called tumor-associated neutrophils (TANS). They are TAN-1 which are cytotoxic for tumor cells.

The other which promotes tumor development metastasis and angiogenesis is TAN2. Neutrophils are known to stimulate the tumor cells to secrete enzymes like matrix metalloproteinase 9 which brings about metastasis reduce apoptosis and induce carcinogenesis[40]. Neutrophils when they release ROS, proteases, and defensins can directly kill targeted cells.

Also, many ways are being forwarded to kill tumor cells by using target-specific antibodies change in the immunity of tumors. Also, by increasing the number of tumors infiltrating neutrophils by using live bacteria like *Mycobacteriumbovis, Corynebacterium parvum.*

Neutrophils can be used for the dung drug delivery system as they enter tumor cells when activated [41].

Cancer niche

The concept was first introduced about 40 years ago. It is an active system consisting of cellular components and cell-secreted function molecules. These have different roles in CSC's self-renewal activation and resistance to the cancer niche [42].

The normal stem cell niche and CSCs differ from each other by the properties and functions of the components of the niche.

- The CSC niche has aggravated state of the components i.e.
  - The tumor-associated fibroblast (TATS).
  - Tumor-associated macrophages (TAM)
  - Tumor-associated Neutrophils
  - Mesenchymal stem cells (MSCs)
- Also, change in cell-mediated adhesion [43].

These are cellular components. The soluble factors are also there in the CSC niche which affects tumor survival and progression coming to the cellular factors.

Tumor-associated fibroblasts (TATS)

- These form the important cellular components of the tumor niche and are the same as IL-6 an important cytokine that can lead to angiogenesis.
- Also, TAFs cause cancer resistance by inducing drug resistance.
- Another important component of the cancer niche is tumor-associated macrophages (TAM) which play a role in cancer progression and metastasis.
- Tumor-associated neutrophils.
- T- regulatory cells [Treg cells are both cells which play a role in the immune response to cancer cells] [44].

Mesenchymal stem cells (MSCs)

This is another vital component of the primary tumor niche which maintains, the CSC population by the activation of the NK-KB pathway via the situation of Ox L12, IL6, IL8 and overexpression of Miri 99a [45].

These help in the renewal of cancer cells and their sustenance and affect the microenvironment by differentiating into TAFs [46].

Cell-mediated adhesion

Adhesion of CSCs to ECM will lead to cancer progression and metastasis also the presence of the cancer niche cells is important for the CSCs to adhere and migrate through hedgehog or notch pathways to other metastatic sites [47]:

- Soluble factors of cancer niche an MMP2,3 and 9 by TAF and TAN leading to metastasis of cancer cells
- Hypoxia will lead to changes in CSCs leading to increased stemness and resistance to therapy.
- Factors released by exosomes lead to the formation of drug-resistant CSCs [48].

Conclusion

There are many factors involved in cancer that play a role in cancer resistance to therapy. Detailed study and modes of modulating the traditional routes of therapy either Radiotherapy or chemotherapy are essential to help patients to have better progress in survival and drug response to cancer. This will bring about better recovery survival and reduce morbidity associated with cancer.

Conflict of Interest

None.

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