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Review

Cancer Stem Cells

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ABSTRACT

Many investigations have been conducted on how cancer develops and how to cure it over the years since the diagnosis of the disease first appeared in medical history. On the basis of securities therapies, numerous treatment modalities have been suggested. The expression of cancer stem cells (CSCs) is a result of the malignant tumor's complete disappearance and propensity to reappear. Self-renewal is the primary hallmark of CSCs. This characteristic explains why to stem cells and cancer cells share some characteristics. Cancer stem cells are hypothesized to be the cause of aggressive, recurring cancers that are resistant to chemotherapy. The study of cell biology in medicine has grown in recent years. Particularly, CSCs are believed to be crucial to tumor spread. Future research will therefore develop medicines that target CSCs for the treatment of cancer by determining the prognosis. This chapter explores the definition and historical background of cancer, along with the definition, history, metabolic features, and other characteristics of CSCs. Additionally, it examines the role of CSCs in conventional cancer treatments.

Keywords: Cancer, cancer stem cells, cancer treatment, tumor-initiating cells.

Tumor-initiating cells (TICs) are another name for cancer stem cells (CSCs). The CSCs sometimes referred to as uncommon progenitor cells, are characterized by highly malignant characteristics. Cancer stem cells with highly malignant traits exhibit resistance to therapeutic drugs. Since the 1990s, anti-neoplastic therapy approaches have been updated and improved with a focus on CSCs, which are the cause of cancer metastasis and residual disease.[1]

It is clear from looking at the history of cancer that it has a very long past. There has been cancer since 4000 years ago. Cancer is a noun that derives from the Latin words "canker" or "carsinos," which signify crab. Tumor is another phenomenon that can be seen in cancer biology. Tumors have been described since the 3rd century BC. Hippocrates was the first person to use the word tumor. This phrase has been compared to crab legs due to how big the veins are. The Greek doctor Galen used the Greek word "oncos", which means swelling. Cancer, in essence, is a disorder in which cells proliferate, develop, and assemble uncontrolled.[2-6]

Modern technology and advancements have led to improvements in cancer therapeutic strategies, however, they are still insufficient. One of the most important concepts in the discipline of stem cell biology is TICs or CSCs. The term "cancer stem cell" first appeared in the scientific literature in 2001. Researchers have shown that some self-renewing cells can organize into colonies or cell communities in the spleen. Several malignant tumor cells injected into the same patient or case can result in the development of new tumors, according to scientific research. Leukemic stem cells are a small fraction of blood cancer cells that are known for pointless growth. For a while, cell subpopulations with comparable traits have been found in a variety of solid cancers, including melanoma, liver cancer, brain cancer, and breast cancer. Cancer stem cells might differentiate and regenerate themselves, just like undifferentiated cells do in tissues. They can differentiate very rapidly, leading to tumor formation, development, invasion, metastasis, and resistance to cancer.[7-12]

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Some tumor cells experience epigenetic changes in signaling pathways that result in CSCs formation as well as genetic changes (such as mutations and gene defects) in these cells. Different cell types, such as undifferentiated cells, progenitor cells, and differentiated cells, are among these variances.[13]

The Origin of Cancer Stem Cells

In 1964, research scientists first demonstrated and proved the relationship between cancer and stem cells. There are active signaling pathways connecting healthy stem cells to CSCs. It has been demonstrated that random mutations or genetic alterations during deoxyribonucleic acid (DNA) self-mapping can cause normal stem cells to develop into CSCs. A research investigation established that adult stem cells cause inflammation and epithelium malignancies due to abnormal stromal signaling.[14,15]

Differentiated Cells

Cancer stem cells can arise from mature cells through three main mechanisms, including genomic instability, gene transfer, and microenvironmental changes.[16,17]

Genomic instability occurs in stem cells, progenitor cells, and differentiated cells. The transformation of the cell through genomic instability is the basis of cancer. This phenomenological approach occurs at the chromosomal and molecular levels, including aneuploidy and point mutations in proto-oncogenes or tumor suppressor genes, respectively. Genomic instability has been proposed as a major problem for tumor formation and cancer initiation.[18,19]

Horizontal gene transplantation or transfer is recognized as an important source of CSCs.[20]

In eukaryotic cells, DNA is transferred from phagocytic and apoptotic cells to recipient cells during phagocytosis via horizontal gene transfer, which modifies the recipient cells' nuclear genomes. This mechanism occurs during the development and tissue repair process and involves integrated DNA transfer, integration, and expression in recipient cells.[21]

Horizontal gene transfer can be mediated by molecular mechanisms. These mechanisms include transduction, conjugation, or transformation.[22]

Tumor cells can phagocytose or take up fragmented DNA molecules that can be transferred to recipient tumor cells. DNA fragments can be absorbed by stem cells, which can result in genetic material modification and the development of CSCs.[21]

The differentiation and transformation of CSCs are influenced by a number of microenvironmental variables. These factors stimulate tumorigenesis. Interleukin (IL)-6, tissue injury, radiation therapy, and toxin exposure, for instance, can cause mutations in the genes encoding the tumor suppressor p53, the Kirsten rat sarcoma viral oncogene homolog (KRAS) protein, and nuclear factor-kappa B (NF-κB).[23]

The stability of both cancers stem cells and non-cancer stem cells is maintained by NF-κB, and the IL-6 produced by CSCs promotes the development of non-CSCs into CSCs.[24]

Metabolic Reprogramming of Cancer Stem Cells

More recently, metabolic reprogramming has been observed to delay the differentiation of CSCs. Normal cells and cancer cells both have been through glycolysis and oxidative phosphorylation, but CSCs have a unique metabolic flexibility. In the presence of oxygen, CSCs maintain homeostasis and alternate between glycolysis and oxidative phosphorylation to aid in the growth and development of tumors. Tissue-specific variations, CSC niche, and heterogeneity are some of the most crucial aspects of the metabolic phenotype of CSCs, including the tumor microenvironment. Investigations have shown that CSCs are either oxyolytic or glycolytic, depending on the study.[25]

PROPERTIES OF CANCER STEM CELLS

Self-Renewal

Cancer stem cells have the ability to self-renew and generate new stem cells in an asymmetric and symmetric manner.[26] The self-renewal mechanism of CSCs has been demonstrated by tumor serial transplantation. In this method, cancer stem cells isolated from a tumor are injected into a mouse model for tumorigenicity testing to examine the ability of isolated cancer stem cells to form a new tumor.[27] Stem cell self-renewal involves several signaling pathways. The proliferation, maintenance of cell lineage, differentiation, and regulation of healthy adult stem cells and cancer stem cells are all critical processes regulated by the Wnt/β-catenin pathway.[28]

The expression of cancer stem cell markers, chemosensitivity, overexpression or aberrant activation of this signaling pathway promotes tumor growth *in vivo* and the ability of cancer cells to self-renew. Wnt/β-catenin regulates markers and

transcription factors such as CD24, CD44, epithelial cell adhesion molecule (EpCAM), and octamer-binding transcription factor 4 (Oct-4).[29,30] Dysfunction or dysregulation of the Wnt/β-catenin signaling pathway has been associated with many types of cancer.[27]

In a pancreatic cancer xenograft model, abnormal expression of the Hedgehog signaling pathway was demonstrated in CD44+ CD24+ ESA+ cancer stem cells. Regulation of messenger ribonucleic acid (mRNA) expression of Hedgehog signaling pathways including SHH, PTCH1, and GLI in gastric CD44+ CD24+ cancer stem cells.[31,32] The proliferation and differentiation of cancer stem cells are also influenced by signaling pathways such as phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR), chromosome 10 deletion phosphatase and tensin homolog (PTEN), bone morphogenetic proteins (BMPs), transforming growth factor-beta (TGF-β), polycomb group B lymphoma Mo-MLV insertion region 1 homolog (BMI1), and Notch signaling pathway (notch1-4/DLL/JAG). Regulatory roles of these signaling pathways in cancer stem cells have been identified in several cancer types.[33,34] In addition, micro RNAs (miRNAs) play a role in the differentiation of cancer stem cells as post-transcriptional regulation. In cancer stem cells, miRNAs target CDK-6, HMGA-2, CDK-4, Notch, E2F3, and BCl2 gene products involved in self-renewal.[35]

Metastasis

Metastasis is also called the secondary stage of cancer. Tumor cells migrate from the cell or tissue they originate from to other tissues or organs through angiogenesis and this is defined as metastasis. Epithelial-mesenchymal transition (EMT) is a process that epithelial tumor stem cells might experience that results in the creation of tumor cells with the ability to self-renew like CSCs. These cells are invasive in that they have renounced cellular connections.[36]

Epithelial-mesenchymal transition is seen as a crucial stage toward metastasis and invasiveness. It has been associated with increased carcinogenesis and upregulated expression of self-renewing CSC markers.[36] However, it is also regulated by environmental factors, miRNAs, signaling pathways, and transcription factors such as Zeb1, Twist1, and Snail1, which promote the loss of epithelial and adhesive properties and the acquisition of invasive and metastatic properties.[37] In primary tumors, these transcription factors have important functions in the invasion, metastasis, and prognosis.[38] micro RNA molecules are characteristically both oncogenic and tumor suppressor genes. These types of miRNA molecules inhibit mRNA processing and therefore increase cellular transformation and tumorigenesis.[39]

Previous studies in science have shown that CSCs can infect certain organs and are intimately linked to metastasis.[40] Many research investigations have suggested that metastatic cells with characteristics of CSCs, such as ALDH+ and CD44+ CD24- in breast cancer, CD26+ in colon cancer, and CD133+ in pancreatic cancer, exhibit this phenotype.[41] Uncertainty surrounds the function of CSCs in premetastatic niche creation and metastasizing to particular organs. It is possible that heterogeneous CSCs with clonogenic capacity and particular phenotypes can metastasize to specific organs.[40]

The role of microenvironmental variables in several malignancies has been established, and it has been found that the brain, lungs, bones, and liver are particularly vulnerable to metastasis and tumor invasion.[41] Exosomes have also been shown to play a part in cancer stem cell-mediated metastasis. Exosomes are cell-derived vesicles containing mRNAs, miRNAs, enzymes, and proteins. Organotropic metastasis may be induced by compounds with integrin protein structures found in tumor exosomes. It has been demonstrated that organ-specific cells can stimulate the premetastatic niche with tumor-derived exosomes. For instance, the exosome integrin molecules 64 and av5, which are enlisted by cells that are localized in the liver and lung, respectively, carry out Src phosphorylation and activate the expression of the pro-inflammatory gene S100, which results in the establishment of premetastatic niches.[42]

Immunological Properties of Cancer Stem Cells

Cancer stem cells have also been found to have immunosuppressive properties like stem cells.[43-45]

T cells, antigen-presenting cells, and natural killer (NK) cells have been demonstrated to be immunosuppressed by the release of IL-4, IL-10, IL-13, and TGF-β by CSCs.[46] Gastric, head and neck, and colorectal carcinoma cases have been shown to have high levels of programmed death ligand 1 (PD-L1) in CSCs.[47-49] PD-L1 has an important function in immunosuppression. Cancer stem cells are more likely to be vulnerable to NK cell-mediated cytotoxicity since major histocompatibility complex I (MHC I) expression is often lower at the cell surface. However, in brain and breast cancers, CSCs are generally deficient in NK-activating ligands such as NKG2D.[51,52]

Colorectal cancer, oral squamous cell carcinoma,

and glioma CSCs are highly sensitive to NK cell cytotoxicity through the expression of various ligands for NK cells.[52] Down-regulation of MHC I in glioblastoma CSCs has also been demonstrated.[46]

Apoptosis

In many therapeutic strategies applied to many types of cancer, apoptosis-related mechanisms or methodologies are applied to tumor cells. However, CSCs use different pathways to escape apoptosis. One of the main methods is the autophagy mechanism in CD133+ CSCs. Autophagy and glucose uptake enhance the growth and survival of CD133+ liver CSCs in hypoxia and low-glucose tumor microenvironments. CD133 released from CSCs stimulates autophagy and glucose uptake, resulting in survival and resistance to apoptosis.[11] By activating CD133+ cells, heat-shock protein 27 (Hsp27), caspase 3, and 9 molecules are deactivated. Therefore, deactivation of the Hsp27 protein molecule sensitizes CD133+ cells to hypoxia and serum depletion-induced apoptosis.[53]

Cell-division cycle protein 20 (CDC20), an apoptosis inhibitor gene, controls the survival of glioblastoma CSCs. CDC20 knockdown is reported to trigger apoptosis in glioblastoma CSCs.[54] It has also been reported that Oct-4 transcriptional factor triggers antiapoptotic conditions in CSCs.[55]

Cancer stem cells and neural stem cells synthesize Sex determining region Y-box 2 (SOX2), which also controls survival expression. Previous studies have shown that epidermal growth factor (EGF) signaling is necessary for the replication and self-renewal of colon CSCs since SOX2 inhibition downregulates survival expression and subsequently mitogen-activated protein kinase kinase kinase kinase 4 (MAP4K4)-induced death.[56,57] As gefitinib, an EGF receptor inhibitor, blocks both the ERK and PI3K/Akt signaling pathways, it increases the susceptibility of colon CSCs to death. In this case, the regulation of apoptosis-related genes was another option involved in the modification of apoptosis in CSCs.[58,59]

Heterogeneity

Previous studies have shown and reported that CSCs have a heterogeneous population and are phenotypically unstable. According to a study, in immunodeficient nonobese diabetic/severe combined immunodeficiency (NOD/SCID) mice, both CD271- and CD271+ melanoma cells create new tumors.[60] Compared to markers such as CD133, CD44, or EpCAM, CD166 is validated as a reliable surface marker for lung CSCs.[61] Cancer stem cells exhibit a different miRNA profile than non-CSCs. For example, while abnormal expression of miR-125b has been linked to stem cell-like side population (SP) in breast cancer[62], abnormal expression of miR-888 was detected in the SP of Michigan Cancer Foundation-7 (MCF-7).[63] More effective markers need to be found and used to identify CSCs and their heterogeneity. Gene expression, proteomic profiling, genetic mutation analysis, and next-generation sequencing are widely applied in cancer biomarker discovery.[64]

Plasticity

Cancer stem cells are altered in terms of plasticity. This transformation occurs between normal somatic cells or between stem cells. Phenotypic plasticity, according to recent scientific research, is a new paradigm for understanding cancer genesis, incidence, progression, and therapeutic strategy development against treatment resistance.[65]

The plasticity phenomenon causes phenotypic heterogeneity of CSCs.[66] One of the most important processes in CSC plasticity is EMT. According to recent scientific research and studies, CSC phenotype types have been obtained mostly in breast cancer.[67,68]

Mesenchymal-epithelial CSCs and EMT CSCs are two different populations of CSCs seen in breast cancer.[69] According to certain studies, non-cancerous stem cells can become CSCs. In breast cancer epithelial cells, the suppression of some tumor suppressor genes, such as PTEN, enhances the stemness of these cells.[70]

THERAPEUTIC APPROACHES TARGETING CANCER STEM CELLS

Cancer Stem Cells and Immunotherapy

Many alternative approaches, including immunotherapy, gene therapy, molecular inhibition, and combination therapy, are being extensively researched since CSCs are resistant to conventional cancer therapies. Immunotherapy has enormous potential to target CSCs.[71] The survival of human epidermal growth factor receptor 2 (HER2)-expressing glioma cells, both CD133+ and CD133-carcinoma cells, was successfully reduced by chimeric antigen receptor (CAR) T cells that were specific for the HER2 protein.[72] In addition, AC133 (an epitope of CD133)-specific CAR T cells destroyed CD133+ glioma CSCs.[73]

According to a different study, most osteosarcoma cancer stem cells that are CD44+ also express CD47. As a result, we employed anti-CD47 to specifically

target CD47 and found that CD47 blockage limits the proliferation and invasion of tumor cells. Similar to this, inhibiting CD47 increased tumor-associated macrophage phagocytosis.[71]

Cancer Stem Cells and Radiation Therapy

Radiotherapy is one of the alternative cancer treatments used today for many types of cancer. Advances in medical imaging and technological dose delivery have opened a new horizon in three-dimensional conformal therapy. Five radiobiological principles DNA damage repair, cell cycle redistribution, repopulation, reoxygenation of hypoxic tumor locations, and radiosensitivity form the basis of conventional radiotherapy. To obtain the maximal level of healing while minimizing normal tissue harm, one must take into account radiosensitivity, a fundamental intrinsic feature of tumor cells.[74]

Research from the past has revealed that compared to other cancer cells, CSCs are more resistant to radiotherapy. They are therefore believed to be to blame for tumor recurrence and therapy failure. Several investigations have demonstrated that radiobiological mechanisms including radiation response are compromised by CSCs. Such reports also assess radiotherapy's present state of understanding and therapeutic approaches.[74]

Even though radiation increases overall survival and quality of life, patients still experience relapses even after complete remission due to intrinsic variables. Several criteria, including findings from some research, suggest that CSCs have high quantities of antioxidants and the ability to repair DNA damage. These factors contribute to the radiation resistance of CSCs.[32,75]

In conclusion, one of the diseases that leads to the greatest fatalities worldwide is cancer. There are various causes that cause cancer, according to studies conducted from the beginning of the recorded history of the disease to the present. Cancer is unavoidable due to a number of factors, including the environment, genetics, epigenetics, and certain medical conditions. Cancer stem cells, also known as cancer-initiating factors, are visible when the occurrence of cancer is examined from a more in-depth perspective. It is well known that CSCs behave just like healthy somatic stem cells. They exhibit traits like proliferative capacity and self-renewal. Conventional cancer treatment strategies are ineffective against cancer stem cells. The cancer's recurrence is one of the key causes of this. The standard treatment for many cancer types is chemotherapy. In situations of cancer, chemotherapy or other forms of treatment (chemoradiotherapy, chemosurgery, etc.) in conjunction with chemotherapy can be effective. The cancer could, however, come back at some point in the future. Such traditional therapy approaches are less effective against cancer that has returned. As a result of their heterogeneity, CSCs are more insensitive to therapies and resistant to them. Alternative therapy modalities should be created, targeted therapies should be researched, CSCs should be separated using pertinent biomarkers, and various therapeutic approaches should be created for CSCs in order to prevent this in the future.

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