Cancer Stem Cells - Recalcitrant Cells

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ABSTRACT

The initiation, growth, recurrence and metastasis of cancer have been recently related to the presence of cancer stem cells (CSCs) within the tumor. CSCs are the distinct sub – population of tumor cells that have the ability to undergo self- renewal and differentiation. They also possess the capacity to promote tumorigenesis and recurrence after treatment. Various hypotheses have been proposed regarding their origin. The aim of this review is to discuss the insights of cancer stem cells and to provide a brief review on their features, origin, methods of their identification, association with signaling pathways, properties which rendering them chemo resistance and radio resistance and the development of new therapies that are targeting these cancer stem cells.

Introduction

Cancer is a large group of diseases characterized by uncontrolled growth and spread of abnormal cells[1]. The progression of cancer is related to the presence of distinct population of cells known as cancer stem cells. American association of cancer research work shop defined cancer stem cells as a cell within a tumor that possesses the capacity to self renew and to cause the heterogenous linages of cancer cells that comprise a tumor.[2] Cancer stem cell theory of tumorogenesis was first described in 1994 in acute myeloid leukemia.1 Accumulated mutations in normal stem cells and their progenitors result in the manifestations of cancer stem cell activity. Several environmental factors and carcinogens cause aberrant mutations which may cause reprogramming of epigenetic mechanism and results in the generation of cancer stem cells.[3] Cancer stem cells are thought to be the source for the tumor survival and the regrowth. E.Allegra in 2012 described the characteristics of CSCs as those which posses anchorage independent growth, metastasting capacity, ability to sustain a long life, self renewal and resistant to damaging agents.[4] Further characterization of cancer stem cells is needed in order to demolish them, which might donate significantly to the therapeutic management of cancers.

Cancer Stem Cell Properties

Stem cells are those cells within organs with the ability to self-renew and give rise to all types of cells within the organ to drive organogenesis. Cancer stem cells are those cells within tumors with the ability to self-renew and give rise to the phenotypically diverse tumor cell population to drive tumorigenesis. Recurrence and metastases of tumor and their cellular heterogeneity might be outcome of cancer stem cell differentiation and asymmetric division of cancer stem cells.

The properties of the cancer stem cell are i) They are small fraction of the cancer cells within a tumor that have tumorigenic potential when transplanted into immunodeficient mice. ii) The CSC sub-population can be separated from the other cancer cells by distinctive surface markers like CD44, ALDH1A1, CD131, CD24 etc. iii) Tumors arising from the CSCs contain the mixed tumorigenic and non-tumorigenic cells of the original tumor. iv) The cancer stem cell sub-population can be serially transplanted through multiple generations, indicating that it is a self-renewing population.[5]

Cancer Stem Cell Hypothesis

Two separate and mutually exclusive models have been developed to explain the development of tumors. The stochastic model postulates that all cells within a tumor contribute in varying degrees to the maintenance of the tumor. The cancer stem cell model states that, they form a distinct subset of the tumor cells, which are eventually responsible for tumor initiation, progression, and recurrence. Through self-renewal and differentiation, CSCs are responsible for the production of various tumor cells and contribute to tumor heterogeneity.[6] Cancer stem cells continue to divide asymmetrically creating initially the two different cell populations. One population retains the self-renewing properties of the parental cancer stem cell while the other population is tumor cell with ability to differentiate but they do not have the ability to initiate tumor growth.[7] Either the stem cell acquires cancer properties or the cancer cell acquires the stemness properties is under debate.

Identification of Cancer Stem Cells

Various methods for identification of CSC sub populations by presence of cell surface and cytosolic proteins by Immunohistochemistry, Isolation and in vitro expansion of cells from tumour specimens, cell sorting by Flow cytometry,[8] Side population Assay, ALDH Activity, Clonogenic Assay, Mesenchymal differentiating culture conditions for Sarcospheres.[9]

Cancer Stem Cells and Signalling Pathways

CSC self-renewal and differentiation is strongly controlled by multiple regulatory mechanisms, including cytokines from the cancer niche. A number of signaling pathways control cancer, which includes the Hedgehog, Notch, and Wnt/β-catenin pathway. Wnt signaling plays an essential role in regulating regulating stem cell function. Wnt binding to Frizzled receptors (Fzd) activates disheveled (Dsh), inactivating GSK3β, thus stabilizing β-catenin, and

thereby inducing target genes. Notch signaling pathway activation contributes to development of a number of stem cells and early progenitor cells. Hedgehog (including Indian hedgehog (Ihh), desert hedgehog (Dhh), and Sonic hedgehog (Shh)) bind the patched receptor (PTCH1), depressing its constitutive repression of smoothened (Smo), leading to activation of the Gli transcription factors.[10]

Why Cancer Stem Cells are Recalcitrant?

Various mechanisms such as drug inactivation, changes in cellular targets, inhibition of drug accumulation and activation has been attributed to the recalcitrant property (resistant or unresponsive to treatment) of CSCs. Drug efflux transporter proteins (ABC transporters) are generally found to be overexpressed in drug-resistant cancer cells. Antiapoptotic signaling pathways are concerned in CSC-mediated drug resistance.[11] Recently, Wnt and β-catenin signaling was suggested to contribute radioresistance for cancer stem cells.[12]

Strategies to Eradicate CSCs

It is obvious that a cancer treatment that fails to get rid of cancer stem cells may allow regrowth of the tumor. In cases of recurrences, where tumor bulk is removed and chemotherapy is given, a likely explanation is that the cancer stem cells have not been completely destroyed. Therapeutic strategies that specifically target cancer stem cells should eradicate tumors more effectively than current treatments and reduce the risk of relapse and metastasis. Targeting various signaling pathways Notch, Wnt, Hedgehog - Deregulation of signaling pathway networks plays an important role in enabling CSCs to retain stem cell properties. The familiar Notch, Hedgehog and Wnt signaling pathways play fundamental roles in maintaining CSC populations. 2) Targeting Reactive oxygen species (ROS) – alters intracellular environment which facilitates apoptotic death signals. 3) Disruption of supporting niche - The tumor microenvironment can create a niche to harbour and protect CSCs from drug-induced apoptosis. 4) Targetting surface antigens, ligands or antibodies against tumor surface makers have been developed to enhance the specificity of therapeutic strategies. Important interest has been generated in the development of monoclon 333333333al antibodies to target CSCs. Monoclonal antibody conjugated to the cytotoxic agent has been developed and widely used to treat AML 5)Blockade of CSC functions, reversal of CSC associated resistance mechanisms.[13] Lamb. R has proposed that antibiotics that target mitochondria can effectively eradicate cancer stem cells, across multiple tumor types.[14]

Conclusion

CSCs are a novel cancer target. Significant links between CSCs, tumor progression, and therapy resistance have necessitates the need for novel therapeutic strategies that target these distinct aggressive cancer subpopulations. Evolution in identifying the CSC-specific surface markers, understanding the mechanism of CSC tumorigenic capacity will be helpful to drive the therapeutic application of targeting these CSCs. Combination therapies targeting CSC and tumor bulk populations are most likely to lead to optimized cancer treatments and to further reduce cancer morbidity and mortality.

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