

The Remedial Anabasis- Cancer Stem Cells

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Keywords

Embryonic stem cells; Embryonal carcinoma cells; Induced pluripotent stem cells; Adult stem cells

Premise and Principle

Emergence of cancer is contemplated as a genetic phenomenon wherein genetic evolution of malignant cells modifies the progression of individual tumour. Genetic mutations are a conjectural phenomenon and unsynchronized mutational configurations can appear. Accumulations of cancer cells articulate a dynamic environment comprised of multiple, heterogeneous tumour cell territories and distinctive molecular signatures pertaining to diverse malignancies with cogent genomic mutations. Fundamental biological processes as designated with committed cancer stem cell lineage, definitive genetic evolution, signalling cascades with explicit oncogenes, modes of neo vascularization and interactions pertaining to tumour cell microenvironment are analysed [1,2]. Stem cell as a terminology was initially adopted by a German biologist "Ernst Haeckel" in 1868. Currently, five principal categories of stem cells are cogitated for therapeutic purposes and defined as embryonic stem cells (ESCs), embryonal carcinoma cells (ECCs), induced pluripotent stem cells (iPSCs), germinal stem cells and adult stem cells (ASCs). Morphological enunciation of a stem cell is designated as a spherical cell with minimal cytoplasm and an enlarged nucleus with elevated nucleus/ cytoplasmic ratio. Several lineage specific biomarkers are available to distinguish the stem cell, however, alkaline phosphatase is discernible in a majority of stem cell categories [1,2]. Embryonic stem cells (ESC) are particular cells which are engendered from inmost cellular aggregates of blastocyst stage of embryonal development. Embryonic stem cells are self- replicating cells and demonstrate a pluripotent capacity with an ability to differentiate into three pertinent germ cell layers. The diverse cell types can be adopted into contemporary methodologies of stem cell therapies. Embryonic stem cells can be supplanted with induced pluripotent stem cells (iPSCs) which are essentially reprogrammed cells engendered from adult somatic cells or cutaneous fibroblasts. Induced pluripotent stem cells recapitulate embryonic stem cells and are devoid of immunogenic features or ethical considerations cogent for stem cell transplantation [2,3]. Foetal stem cells can be harvested from placenta, amniotic membranes, amniotic fluid or foetal tissues and display an enhanced capability of maturation and differentiation, in contrast to stem cells obtained from adult tissues. Somatic stem cells (SSCs) or adult stem cells (ASCs) can further differentiate into neural stem cells (NSCs), mesenchymal stem cells (MSCs), haematopoietic stem cells (HSCs), endothelial progenitor stem cells (EPCs) and adjunctive cells. Adult stem cells are beneficial for adequate regeneration and replacement of soft tissues and are considered a preferential therapeutic modality for the discipline of regenerative medicine [2,3] [Table 1]. Cancer stem cells are tumour propagating cells which delineate varying characteristics including self-renewal. Cancer stem cells (CSCs) contribute as a miniature proportion of malignant tumours. Cancer stem cells can enunciate potential and impeding differentiation towards heterogeneous tumour cell colonies and account for tumour reoccurrences and inferior response to therapy with eventual evolution of therapeutic resistance. Cancer stem cells are situated in and harvested from diverse tumour tissues as associated with carcinoma breast, colorectal carcinoma or carcinoma pancreas. Aforesaid stem cells demonstrate distinct biophysical properties and response to diverse treatment methodologies, in contrast to accompanying terminally differentiated cancer (TDC) cells [3,4]. **Avant-Garde Approach** Cancer stem cells commonly depict an immortal phenotype and can initiate a tumour reoccurrence. Categorical varieties of cancer and relapses can be engendered following administered chemotherapy and/or radiotherapy. Apart from self renewal and differentiation, stem cells demonstrate unique attributes such as migration towards cancer cells, anti-tumour activity, secretion of bioactive molecules and immune suppression. Aforesaid properties promote the isolation and targeting of tumour cells and circumvent impediments to effective and contemporary gene therapy [4,5]. Cancer cells originating from progenitor cells or preliminary stem cells can induce a precipitous metastasis and tumour cell deposits with extensive genetic heterogeneity. Metastasis

Article Information

DOI: 10.31021/brr.20192111
Article Type: Review
Journal Type: Open Access
Volume: 2 Issue: 2
Manuscript ID: BRR-2-111
Publisher: Boffin Access Limited

Received Date: 25 September 2019

Accepted Date: 09 October 2019

Published Date: 14 October 2019

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Citation: Anubha B. The Remedial Anabasis- Cancer Stem Cells. Biomed Res Rev. 2019 Oct;2(2):111

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generated from late- appearing stages of stem cells are homogenous and exhibit limited potential for tumour dissemination. Tumour heterogeneity and a penchant for distant metastasis is contingent to differentiation and/ or dedifferentiation of cancer stem cells. A significantly advantageous therapeutic prototype can be obtained with the process of targeting cancer stem cells rather than terminally differentiated stem cells for the purpose of tumour attenuation and shrivelling. Satisfactory cancer treatment mandates comprehensive elimination of a cellular tumour. Thus, a combination treatment modality with the potential to target cancer stem cells and abutting or distant tumour mass can be contemplated as an efficacious and cogent clinical and therapeutic strategy [3,5]. Stem cells enunciate growth factors and cytokines which regulate innate and cellular immune pathways of the host. Stem cells can be distinctly manipulated in order to circumvent the immune response mounted by the host and can function as a cellular agents for therapeutic deliverance. Stem cells exemplify intrinsic, tumour- tropic attributes on account of incumbent chemokine- cancer cell interaction. Neural stem cells and mesenchymal stem cells can actively secrete enzymes which metamorphose non- toxic prodrugs into cytotoxic compounds. Modifications encountered within the stem cells can assist their localization into specialized tumour tissue where exogenously secreted enzymes transform the prodrug into cytotoxic molecules which culminates into deterioration of tumour cells. The quantification, timing and site of cytotoxic drug delivery can be regulated with accuracy. Employment of aforementioned enzyme/ prodrug treatment is also termed as "suicide gene therapy" [2,3]. Stem cells can fulfil the objective of in-situ drug repositories with the elucidation of anti-tumour agents for prolonged duration, a feature which surmounts the limitations of varied cancer therapy regimens such as increasing systemic toxicity and a reduced half life of administered drugs. TNF α - related apoptosis- inducing ligand (TRAIL) appears to be a predominantly applicable, secreted agent which induces apoptosis of cancer cells. Stem cells can be suitably altered to transport growth inhibitory proteins such as interferon β which creates a tissue microenvironment essentially non-conducive for tumour progression. Oncolytic viruses can subjectively propagate tumour cells. Neural stem cells transduced with oncolytic viruses can competently adhere to malignant cells. Thus, neural stem cell delivered tumour oncolytic viruses delineate superior anti- tumour consequences, in contrast to singular therapeutic adoption of oncolytic viruses [2,3]. Stem cells can be utilized as delivery agents for nano-particles which are beneficial in instances of failure to localize micro-metastatic lesions or in individuals with ineffective dissemination of solid tumours or managing associated therapeutic restrictions. Carriers of essential nano- particles are frequently constituted of elevated concentration of insoluble chemotherapeutic agents and can prevent therapeutic degradation. Evolving diagnostic methodologies such as next generation genetic sequencing and cancer genomic analysis can ensure an accurate and efficacious therapeutic targeting with the employment of cancer stem cells. Sequencing technologies employing singular cells and adoption of spatial transcriptomics are cogent for precision based profiling of individual tumour cells exemplifying specific genetic and epigenetic cellular hierarchy [6,7]. Contemporary and versatile gene editing techniques as adapted with CRISPR /Cas9 mechanisms can be employed. Cancer stem cells and cancer stem cell initiated tumour cell lineage specific potent and particular molecular signatures, as cogitated with particular genetic mutations, genomic and protein expression, regulation of micro-RNA, DNA methylation and pertinent modification of histones, can be suitably discerned and edited with an appropriate interpretation in order to configure targeted and immune based cancer therapies [1,2] (Figures 1-4).

Dilemmas and Drawbacks

Transplanted stem cells can undergo a malignant transformation. While engaging into tumour-specific microenvironment, categorical stem cells can develop into cancer supporting cells and correspondingly amalgamate and enhance malignant cells. The

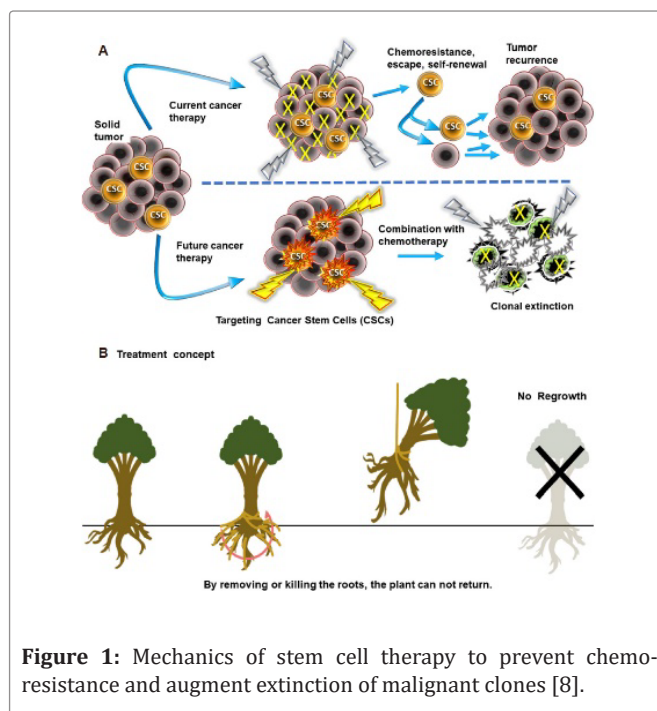


Figure 1: Mechanics of stem cell therapy to prevent chemo-resistance and augment extinction of malignant clones [8].

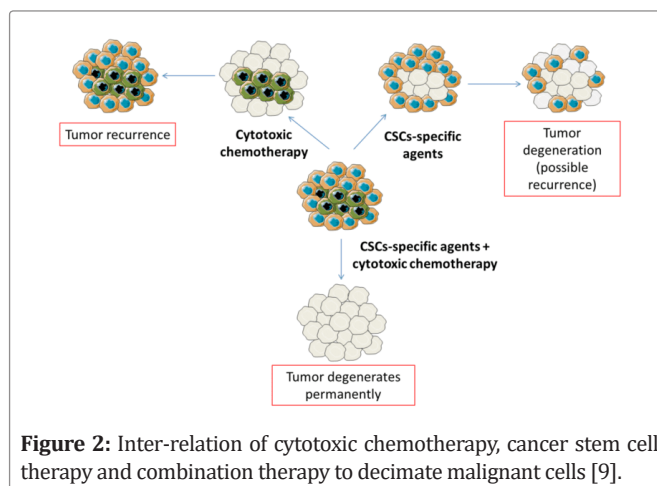


Figure 2: Inter-relation of cytotoxic chemotherapy, cancer stem cell therapy and combination therapy to decimate malignant cells [9].

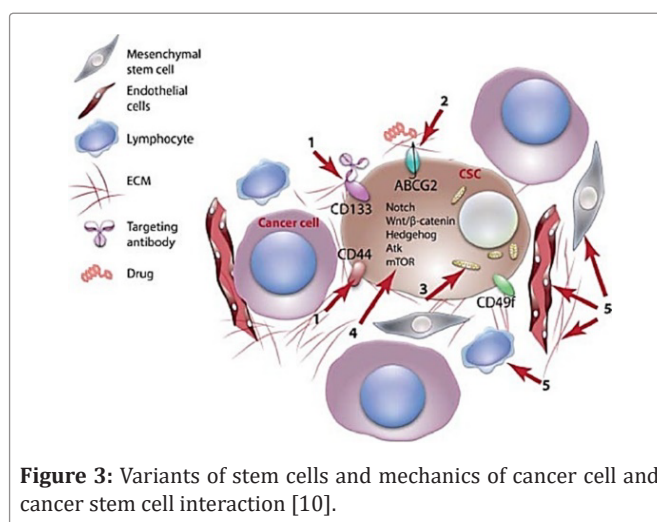
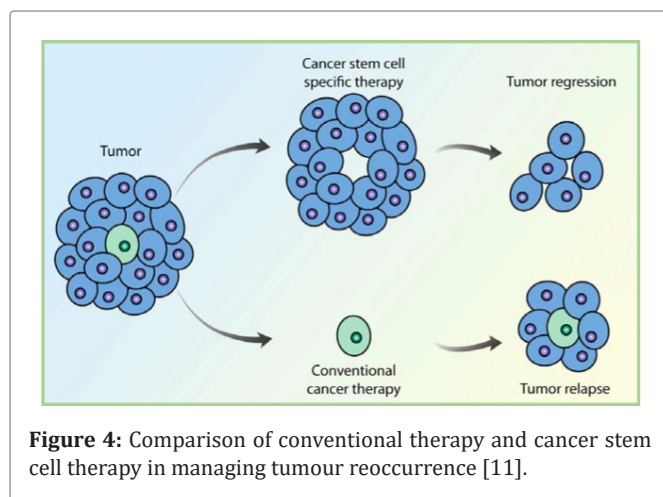


Figure 3: Variants of stem cells and mechanics of cancer cell and cancer stem cell interaction [10].

versatile interaction between tumour cells and definitive stem cells requires evaluation when contemplating the efficacy of anti-tumour therapy with stem cells. Stem cells can be effectively utilized as a therapeutic agent for treating cancer. Nevertheless, employed stem cells can enhance tumour progression and evolution. Acceptable



Methodologies	Malignancies	Modifications
Enzyme/ Prodrug Therapy	Glioma	Oncolytic virus transduced NSCs, MSCs
	Colon adenocarcinoma	Oncolytic virus transduced NSCs
	Metastatic and primary pulmonary carcinoma	Engineered NSCs
Secreted Agents	Glioma	Oncolytic virus transduced NSCs, Engineered NSCs
	Brain metastasis from carcinoma breast	Oncolytic virus transduced NSCs,
	Carcinoma breast	Engineered MSCs
Viral Therapy	Hepatocellular carcinoma	Virally infected MSCs
	Glioma	Infected NSCs & MSCs
Nanoparticle carriers	Solid tissue tumours	Loaded NSCs
	Glioma	Loaded MSCs
Regenerative Medicine	Haematological malignancies	HSCs (allogenic transplantation)
	Liver disease	engrafted iPSCs
Immunotherapy	Solid tissue tumour	HSCs (graft induction vs tumour effect)
	Lymphoma	HSCs(allogenic transplantation,) iPSCs (T cells)
	Melanoma	Engineered HSCs
Targeting CSCs	Glioma	Modified HSCs
Anticancer drug screening		Cancer tissue derived iPSCs(cellular targets)

NSC; Neural stem cell, MSC; Mesenchymal stem cell, HSC;
Haematopoietic stem cell, iPSC; induced pluripotent stem cells

Table 1: Stem Cell Applicability in Cancer Therapy [3].

stem cell therapies can encounter immunological rejection. Therefore, recipients of essential stem cell therapy necessitate the administration of efficacious immune suppressive regimen with a consequent emergence of secondary, opportunistic infections [6,7].

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8. Image 1 Courtesy :Journal of Cancer Metastasis and Treatment
9. Image 2 Courtesy :Research Gate
10. Image 3 Courtesy :Technol Cancer Res Treatment
11. Image 4 Courtesy: Harvard Stem Cell Institute