

The Winner of the Contest to Eradicate Cancer Stem Cells Wins the Contest of Cancer Therapies: The Winner is Cell Differentiation Agent Formulations

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Opinion

Cancer stem cells are very likely to originate from progenitor stem cells

It has been widely accepted that most human cancers had a small subpopulation of cancer stem cells (CSCs) which were closely related to progenitor stem cells (PSCs) based on cell features and biological missions. These cells express ATP binding cassette drug pump that can effectively exclude toxic materials and have activation of anti-apoptosis programs that negate the pro-apoptotic signals activated by DNA damaging agents [1-4]. Thus, these cells are resistant to cytotoxic drugs and radiation. These cells normally reside in acidic and hypoxic microenvironment hard to reach by the blood stream. Like PSCs, CSCs may remain dormant unless situations arise that stimulate their recruitment, such as cytotoxic chemotherapy.

Both CSCs and PSCs express increased levels of telomerase, as do embryonic stem cells and most cancer cells. Methylation enzymes (MEs) of telomerase-expressing cells exhibit altered and enhanced enzyme kinetics due to their association with telomerase [5]. MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomosysteine hydrolase (SAHH) [6]. MEs function as a switch to turn on stem cells to replication or to turn off replicating cells to terminal differentiation (TD) [7]. Normal MEs are subject to regulation by steroid factors via their receptor SAHH. Abnormal MEs lock the switch in the "on" position to block TD. PSCs and embryonic stem cells can carry out differentiation programs despite blockade of differentiation by abnormal MEs, relying on ten eleven translocation (TET) enzymes to achieve DNA hypomethylation to activate differentiation related genes. TET enzymes oxidize 5-methylcytosines (5mCs) and promote locus-specific reversal of DNA methylation. TET genes, and especially TET2, are frequently mutated in various cancers, but how the TET proteins contribute to prevent the onset and maintenance of these malignancies is largely unknown. Tet enzymes are either silenced by promoter methylation or dysfunctional due to mutation in most human cancers [8-10]. The loss of TET enzymes is a hallmark of CSCs that differentiates them from PSCs. The expression of telomerase to convert MEs to abnormally active state can be considered as the first hit of the two hits carcinogenesis theory of Knudson [11]. The second hit to eliminate TET enzymes completes the carcinogenesis process. PSCs are, therefore, literally semi-CSCs. It is much easier to achieve one more hit to convert PSCs to CSCs than to sustain two hits for the conversion other stem cells to CSCs. Besides, other stem cells may not have the features such as drug resistance to become CSCs. Myelodysplastic syndrome (MDS) is a classic case of CSCs originated from PSCs [7]. Evidence suggests that glioblastomas, colon cancer and hepatoma may also originate from PSCs [12].

MDS as a classic disease for the evaluation of drugs against CSCs

MDS is a disease attributable entirely to CSCs [13]. The option to eradicate CSCs is rather limited because of drug resistance and anti-apoptosis capability of CSCs. Drugs effective against CSCs must be natural metabolites or their analogs that can affect abnormal MEs or vital growth signals of CSCs. Thus far, vidaza and decitabine are the two hypomethylating agents approved for the therapy of MDS in the USA. CDA-2 is a hypomethylating agent approved for the therapy of cancer in China [14], which has shown promising therapeutic effect on MDS [15,16]. Vidaza and decitabine achieve DNA hypomethylation by promoting covalent bond formation between DNA methyltransferase and the azacytosine base incorporated into DNA to titrate out methyltransferase [17], whereas CDA-2 achieves DNA hypomethylation by converting abnormal MEs to become normal MEs. An abbreviated clinical trial of CDA-2 for MDS therapy was conducted on 117 patients in China as above described. Based on two cycles of treatment protocols, CDA-2 yielded a slightly better therapeutic efficacy under cytological evaluation, and a markedly better therapeutic efficacy under hematological improvement evaluation in comparison to vidaza and decitabine. CDA-2 is definitely a better drug for the therapy of MDS. It has better therapeutic efficacy and devoid of serious side effects, whereas vidaza and decitabine are proven carcinogens [18,19], and damaging to DNA [20]. It has been reported that vidaza was very toxic to embryonic cells, particularly cardiomyocytes [21].

The active components of CDA-2 are differentiation inducers (DIs) and differentiation helper inducers (DHIs). DIs are chemicals capable of eliminating telomerase from abnormal MEs. DHIs are inhibitors of the individual enzymes of the ternary MEs, which can greatly potentiate the activity of DIs. We have made a variety of different cell differentiation agent (CDA) formulations for the therapy of CSCs enriched cancers untreatable by cytotoxic chemotherapy and radiotherapy [12]. Chemo-surveillance through CDA metabolites is actually the nature's choice to combat cancer [7].

Differentiation therapy employing CDA formulations is compatible to the cell killing therapy on hematological cancers. The therapeutic end point in both cases is based on the disappearance of cancer cells, which are morphologically distinguishable from terminally differentiated cells. The therapeutic end point for solid tumors is the disappearance of tumor. The disappearance of tumor is valid for the evaluation of cell killing therapy but is not appropriate for the evaluation of differentiation therapy which is aimed to turn cancer cells to become terminally differentiated cells no longer capable of replication. Therefore, some adjustment is necessary for the evaluation of therapeutic efficacy of CDA formulations. The disappearance of circulating CSCs is a more appropriate end point. Stabilization of tumor and general improvement of health are also important criteria of therapeutic efficacy.

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