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Wound Unhealing as a Grave Issue of Cancer

Ming C. Liau [a*], Christine L. Craig [a] and Linda L. Baker [a]

[a] CDA Therapeutics, Inc., 3308 Sky Run Court, Missouri City, TX 77459, USA.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Commentary

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ABSTRACT

Wound healing requires the proliferation and the terminal differentiation of PSCs, the most primitive stem cells expressing abnormal differentiation enzymes (MEs). Wound if not healed properly, PSCs may be forced to evolve into cancer stem cells (CSCs), and then to progress to faster growing cancer cells (CCs). Our carcinogenesis studies revealed that the numerous tiny preneoplastic hyperplastic nodules appeared in response to carcinogen challenge were the attempt of the liver to repair the damages created by carcinogen. These nodules represented the proliferation of PSCs displaying abnormal MEs. Most of these nodules disappeared when the damages were repaired. Only a few nodules which were not successful repaired, later developed to become large carcinomas. The employment of phenylacetylglutamine, which was an effective anti-cachexia chemical to protect the functionality of chemo-surveillance, could prevent carcinogenesis induced by potent carcinogens. These studies clearly demonstrated that carcinomas developed if wounds were not efficiently healed.

Perpetual proliferation of CCs was the most outstanding feature of cancer. Stop proliferation of CCs naturally became the top choice of cancer therapy. There were two options to stop proliferation of CCs: one by killing of CCs and the other by induction of terminal differentiation of CCs. Cancer was also made up by CSCs as a minor component. The option by killing of CCs was the choice of cancer establishments, which displayed the feature as anti-wound healing, clearly a

**Corresponding author: E-mail: mingliau@yahoo.com;*

wrong choice because cancer was caused by wound unhealing. The option by the induction of terminal differentiation was the choice of the nature which created chemo-surveillance to ensure perfection of wound healing to avoid cancer. This option displayed the feature as pro-wound healing, clearly the right indication of cancer therapy. CSCs play a major role on the fatal effects of cancer. The effectiveness of cancer therapy depends heavily on the ability to eradicate CSCs. Therapies based on killing of CCs were ineffective against CSCs because these cells were protected by drug resistance and anti-apoptosis mechanisms, whereas the induction of terminal differentiation was a critical mechanism of wound healing very effective to eradicate CSCs. Thus, the option by the induction of terminal differentiation was the right choice for cancer therapy.

Keywords: Cancer moonshot; cancer therapy; terminal differentiation; CDA formulations; CSCs; PSCs; wound healing.

1. INTRODUCTION

Cancer is the leading causes of death worldwide. In 2018, there were 18.1 million new cases and 9.5 million cancer related deaths worldwide [1]. Both cancer incidence and mortality are on the way up by an increment of approximately 0.5 million per year. The NCI prediction is very precise as the cancer deaths in 2019 were exactly 10 million, an increment of 0.5 million. The progress of cancer therapy is very slow despite a major thrust declaring the war on cancer was initiated by President Nixon in 1971 [2]. We have attributed the slow progress to the pursuance of wrong approach on cancer therapy [3]. Cancer is caused by wound unhealing. The therapies based on the killing of CCs create more wounds to aggravate the already badly damaged chemo-surveillance. The contribution to damage chemo-surveillance and the ineffectiveness on CSCs lay the ground for the proliferation of CSCs in order to repair the damages created by cytotoxic agents. Eventually CSCs will reach a level unresponsive to further treatments [4]. The practices based on the killing of CCs must be drastically modified to save cancer patients.

The concept of cancer as wound unhealing was first introduced by the great German scientist Virchow in the 19th century [5]. It was again brought up by Dvorak in 1986 [6]. The close relationship between cancer and wound healing was noticed by MacCarthy-Morrough and Martin [7]. We provided the most important details on this subject that included abnormal MEs to block differentiation [8-10]; chemo-surveillance as a natural mechanism to ensure perfection of wound healing to avoid cancer [11-14]; differentiation inducers (DIs), which are chemicals capable of eliminating telomerase from abnormal MEs, and differentiation helper inducers (DHIs), which are inhibitors of MEs capable of potentiating the activity of DIs, as wound healing metabolites and as the active players of chemo-surveillance [12-14]; hypomethylation of nucleic acids as the most critical mechanism for the induction of differentiation [15]; the mechanism of wound healing to involve the proliferation and the terminal differentiation of PSCs [16-18]; and the evolution of CSCs from PSCs due to wound unhealing [19-21]. Our studies clearly establish that wound healing is a very important health issue, so that the nature creates chemo-surveillance to ensure perfection of wound healing to avoid bad consequences such as tissue fibrosis, dementia, and the worst cancer [17,22,23]. Therefore, the protection of the functionality of chemo-surveillance is very important to avoid devastating diseases such as tissue fibrosis, dementia and cancer. Wound healing process definitely offers the most appropriate solutions of such devastating diseases [24].

2. COMMENTARIES AND DISCUSSION

2.1 Carcinogenesis Studies Revisited

When we carried out carcinogenesis studies during the era between 1979 to 1990, the involvement of wound healing on carcinogenesis was totally unknown, the mechanism of wound healing was also unknown, and CSCs were none existing [25-27]. We have made several unexplainable observations at that time, which can be satisfactorily explained now. During challenge with hepatocarcinogens, numerous tiny preneoplastic hyperplastic nodules appeared which later disappeared. These hyperplastic nodules displayed abnormal methylation enzymes, which must represent the proliferation of PSCs in an attempt to repair the damages created by carcinogens. PSCs express abnormal MEs. Most damages could be repaired and the

nodules disappeared. Only few nodules which did not repair satisfactorily later developed to become large hepatocarcinomas.

Antineoplaston A10 was the code name of phenylacetylglutamine used in Burzynski Research Institute, which did not have remarkable biological effects on cultured cells. This chemical, however, was very effective to prevent the excessive excretion of peptides often observed in cancer patients [11]. The capability of Antineoplaston A10 as chemo-preventive agent could be attributed to its effect to protect the functionality of chemo-surveillance. Therefore, chemo-surveillance is indeed a very effective mechanism to ensure wound healing to prevent carcinogen induced cancer.

Cell differentiation agent (CDA) was a term we created to designate preparations containing DIs and DHIs capable of inducing terminal differentiation of cells expressing abnormal MEs [28].

Abnormal MEs are crucial for rapid accumulation of cells needed for the development of fetus and for the repair of wounds. These normal primitive stem cells express TET-1 enzyme that can cause DNA demethylation to achieve lineage transitions [29]. When a wound is created, it produces particular symptoms, e.g. anemia in the case of myelodysplastic syndrome (MDS) or white lung in the case of COVID-19. The symptom created by the wound will put a pressure for PSCs to proliferate in order to heal the wound to remove the symptom. The proliferation of PSCs, which are normal stem cells, is limited by contact inhibition. That explains the production of numerous tiny hyperplastic nodules during the initial response to carcinogen challenge. TET-1 must be silenced for PSCs to evolve to become CSCs in order to escape contact inhibition. The silencing of TET-1 is a process to achieve malignant transformation [19-21]. CSCs can only be induced to undergo differentiation by CDA. The failure of wound healing in most instance is caused by the deficiency of CDA rather than the deficiency of PSCs which are well protected by drug resistance and anti-apoptosis mechanisms. The proliferation of CSCs still cannot solve the symptom created by the wound because CSCs cannot undergo terminal differentiation in the absence of CDA. Then the pressure will build up to force chromosomal abnormalities to activate oncogenes and/or to inactivate suppressor genes, eventually pushing CSCs to evolve into faster growing CCs.

DIs and DHIs are produced by human body to maintain a steady level of CDA in healthy state [11]. Pregnenolone is an important DHI [30]. The production of pregnenolone is bell shape in relation to ages, peaking at 20-25 years with daily production of around 50 mg [31]. The very young and the very old ages produce relatively little amounts, and these are two age groups most vulnerable to cancer development. The importance of efficient wound healing to the prevention of cancer is quite obvious [12-14]. Cancer establishments totally ignore chemo-surveillance. They approve toxic agents for the therapy of cancer, which are quite harmful to chemo-surveillance. Toxic agents produce wounds to trigger immunological response, which prompts the production of cytokines [16]. Tumor necrosis factor (TNF) among cytokines is very harmful to chemo-surveillance. TNF is also named cachectine after its effect to cause cachexia symptoms. A manifestation of cachexia symptoms is the excessive excretion of low molecular weight metabolites. DIs and DHIs that play important roles of chemo-surveillance are among such low molecular weight metabolites excreted, resulting in the collapse of chemo-surveillance to result in the development of cancer. The contribution to the damage of chemo-surveillance by cytotoxic agents and the ineffectiveness of these agents on CSCs are the reasons cancer therapies based on killing of CCs are unable to win the war on cancer. Restoration of the functionality of chemo-surveillance is an absolute necessity for the long lasting remission. Therefore, only the early stage cancer patients whose chemo-surveillance has not yet fatally damaged can benefit from therapies based on the killing of CCs. The restored chemo-surveillance can subdue surviving CSCs. If chemo-surveillance has been fatally damaged, even fortunate cancer patients reaching complete remission will eventually succumb to recurrence [18].

2.2 Effectiveness of Cancer Therapy Depends Heavily on the Ability to Eradicate CSCs

Cancer establishments have a tendency to pay attention to more visible but not quite essential issues and neglect less visible but very critical issues. Studies of aberrant tRNA methylation were a fashion in a few years span around 1966, and studies of aberrant DNA methylation were another fashion in a few years span around 1985 [22]. Cancer establishments put all efforts on the analyses of methylated tRNA and DNA, and

totally neglected the very critical issue of abnormal MEs. Had they focused the attention on abnormal MEs, cancer was solved in these two periods, immediately before and after the declaration of war on cancer when the solution of cancer was hotly pursued. Likewise, they paid attention on the elimination of CCs and totally neglected the more critical issue of CSCs. CSCs constitute only a small minority, usually less than 2% of most popular cancers. But they are responsible for metastasis, recurrence, drug resistance, and angiogenesis, namely the most fatal effects of cancer. Cancer establishments approved cytotoxic drugs to kill CCs, but in the process these drugs destroy chemo-surveillance that can prevent the proliferation of cells with abnormal MEs, and to promote the proliferation of CSCs, eventually leading to the death of cancer patients [4,32,33]. They also set up disappearance of tumor as a rule to monitor the progress of cancer therapy, which in essence blocked the development of good cancer drugs such as CDA that could come to the rescue of damages created by cytotoxic drugs. The therapies advanced by cancer establishments end up causing the deaths of cancer patients instead of saving their lives. The prediction of yearly increment of 0.5 million cancer deaths worldwide by NCI reflects the inability of current practices to save cancer patients [1]. We must drastically modify the current practices to save cancer patients. The approval of drugs effective on CSCs is imminently important to save cancer patients.

2.3 MDS as a Litmus Test for Cancer Drugs Effective against CSCs

MDS is a classic disease to result from wound unhealing. MDS often starts with a display of an immunological disorder [34] which prompts the patient to produce an elevated level of TNF critical to the development of the disease [35]. It causes excessive apoptosis of bone marrow stem cells, thus severely affecting the ability of the patient to produce hematopoietic cells such as erythrocytes, platelets, and neutrophils. TNF also causes the collapse of chemo-surveillance as above described to result in the evolution of CSCs from PSCs. MDS is at the stage of building up of CSCs unable to undergo terminal differentiation [36]. MDS is a disease attributable entirely to the propagation of CSCs, a classic case of wound unhealing. The therapy of MDS requires the induction of differentiation of pathological cells to become functional erythrocytes, platelets, and neutrophils. CDA-2 was a preparation of wound healing metabolites purified from urine [28], which has been approved for the therapy of MDS in 2017 by the Chinese FDA [29]. Vidaza and decitabine are two drugs approved for the therapy of MDS by the US FDA. When tested under the same protocol, CDA-2 had a slightly better efficacy than vidaza and decitabine based on cytological evaluation, and a markedly better efficacy than vidaza and decitabine based on hematological improvement evaluation, namely no longer dependent on blood transfusion [29]. CDA-2 was totally devoid of serious adverse effects, whereas vidaza and decitabine were known carcinogens [37,38], and very toxic to DNA [39-41]. Clearly, CDA-2 is the drug of choice for the therapy of MDS, which definitely has a better therapeutic efficacy and without adverse effects. All three drugs achieve therapeutic effect by the induction of terminal differentiation of CSCs, CDA-2 by destabilization of abnormal MEs, whereas vidaza and decitabine by titrating out methyltransferase through covalent bond formation between 5'aza-deoxycytosine base incorporated into DNA and methyltransferase. It appears that the induction of terminal differentiation of CSCs is the best strategy to eradicate CSCs. This is the mechanism of wound healing. The process of wound healing is, therefore, the most appropriate modality of cancer therapy [19,22,24,30,42,43]. By holding the key to solve CSCs, we are in the best position to fulfill cancer moonshot of President Biden and to win the war on cancer of President Nixon [44,45].

We have carried out extensive studies of natural and unnatural DIs and DHIs, which can be used to formulate effective CDA formulations according to the formulas previously published [22,29,30,46-48]. We recommended two sets of DI-DHI combinations, one set to target CSCs using natural metabolites arachidonic acid-pregnenolone, and another set to target CCs using unnatural products BIBR 1532-pyrvinium pamoate. The reason for the necessity of two sets is in consideration of drug resistance mechanism of CSCs to reject the accessibility of unnatural products and the enrichment of salvage enzymes of CCs to promote faster growth which may cause rapid degradation of natural metabolites. In addition to DIs and DHIs, we also recommended to use phenylacetylglutamine as an anti-cachexia chemical to improve the therapy, which could be administrated separately as a capsule preparation and monitored independently on the restoration of the functionality of chemo-

surveillance. The therapeutic effect of CDA formulations and anti-cachexia preparation should be monitored separately, because the therapeutic effects are achieved by different mechanisms. The restoration of the functionality of chemo-surveillance can definitely improve the therapeutic effect of CDA formulations. For the evaluation of the therapeutic effect of CDA formulations, we cannot rely on radiological measure of tumor size. Measurements of tumor markers or circulation CCs and CSCs may provide accurate assessments. Studies must be conducted to provide easy and accurate methods. Acceptable procedures definitely will be more difficult than radiological images. As to the assessment on the restoration of the functionality of chemo-surveillance, quantitative assays of plasma and urinary peptides of our previously studies is adequate [11]. Quantitative assays of critical active components such as pregnenolone, uroerythrin, or arachidonic acid may also provide accurate assessments.

3. CONCLUSION

Our previous carcinogenesis studies revealed that PSCs were actively involved in the repair of damages created during the initial stage of carcinogen challenges. The administration of phenylacetylglutamine, which was an effective anti-cachexia chemical, to protect the functionality of chemo-surveillance could effectively prevent carcinogenesis. Inability to repair wounds due to the collapse of chemo-surveillance plays an important role in the evolution of cancer. Thus, promotion of efficient wound healing is an effective approach for cancer therapy. This strategy displays the feature of cancer therapy as pro-wound healing. The strategy of cancer therapies approved by cancer establishments is based on the killing of CCs, which displays the feature of cancer therapy as anti-wound healing, exactly opposite to the process of wound healing. Cancer therapy has been dominated by anti-wound healing strategy unable to save cancer patients, because this strategy contributes damages to chemo-surveillance and is ineffective on CSCs. Pro-wound healing strategy is the right approach of cancer therapy, which is effective to eliminate both CSCs and CCs by inducing these cells to undergo terminal differentiation, and to restore the functionality of chemo-surveillance. By inducing terminal, this therapy can also put to rest chromosomal abnormalities responsible for the activation of oncogenes and inactivation of suppressor genes. Gene therapy to correct chromosomal abnormalities is an attractive cancer therapy, but is very difficult to achieve.

CDA formulations of pro-wound healing strategy are our best hope to achieve the cancer moonshot of President Biden and the war on cancer of President Nixon.

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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