

Restoration of Chemo-surveillance as a Top Priority to Save Cancer Patients

ABSTRACT

Cancer mortality is very high and is still increasing. The objective of this study is to rely on the restoration of chemo-surveillance to reduce cancer mortality called for by President Biden in his cancer moonshot initiative speech last year. The reason cancer mortality remains so high is that we are not pursuing the right approach to cancer therapy. Cancer is caused by wound unhealing due to the collapse of chemo-surveillance. Chemo-surveillance is the nature's creation of allosteric regulation to keep cells with abnormal methylation enzymes (MEs) under control. Wound healing comes naturally because nature creates chemo-surveillance to ensure the perfection of wound healing. Wound healing requires the proliferation and the terminal differentiation of progenitor stem cells (PSCs). Efficient differentiation of PSCs is a critical mechanism of wound healing. MEs play an essential role in the regulation of cell replication and differentiation. In telomerase-expressing cells, MEs are associated with telomerase to alter the kinetic properties of MEs and the regulation in favour of cell growth, which is important for wound healing. Chemo-surveillance is an important safety mechanism to avoid unnecessary build-up of cells with abnormal MEs to cause clinical symptoms such as tissue fibrosis, dementia, organ failure and cancer. Chemo-surveillance can be destroyed under pathological conditions producing elevated tumor necrosis factor (TNF) to cause cachexia symptoms resulting in the collapse of chemo-surveillance. PSCs are then forced to evolve into cancer stem cells (CSCs) by a single hit to silence the TET-1 enzyme to escape contact inhibition which limits the extent of PSCs to build up. The inability of CSCs to undergo terminal differentiation due to the collapse of chemo-surveillance eventually forces CSCs to progress to faster-growing cancer cells (CCs) through chromosomal abnormalities such as translocations or deletions to activate oncogenes or to inactivate suppressor genes to become full-blown cancer. Obviously, the collapse of chemo-surveillance is a critical event in the development of cancer, restoration of chemo-surveillance is, therefore, an easy and effective solution to save cancer patients.

Keywords: allosteric regulation; chemo-surveillance; cancer therapy; CSCs; PSCs; wound healing.

1. INTRODUCTION

Cancer mortality remains at a historical high. According to NCI experts, the cancer incidence was 18.1 million and the cancer mortality was 9.5 million worldwide in 2018. which were on the way to increase with an annual increment of 5% [1]. Cancer incidence and mortality of USA were also on the way to increase. According to the American Cancer Society's statistics, during

the three-year periods from 2019 to 2022, cancer mortality increased from 1.76 million to 1.90 million with an annual increment of 2.7%, whereas the cancer mortality increased from 0.607 million to 0.609 million with an annual increment of 0.1%. Obviously, cancer therapies in practice are unable to bring down cancer mortality. Cancer therapies based on the killing of CCs were the choice of cancer establishments in the past to combat cancer, which have been drilled through as a presidential project during 1971-1976, but failed to achieve the goal of putting cancer away [2]. Despite the failure, cancer establishments were trapped in the failing strategy of killing CCs to combat cancer, although they did make attempts to modify the killing of CCs by more specific approaches such as gene and targeted therapies, anti-angiogenesis agents, and immunotherapeutic agents [3]. The modification of killing strategies may reduce adverse effects but does not help to reduce mortality. Cancer therapies based on the killing of CCs are not a good choice, because such therapies can only benefit the minority of early-stage cancer patients whose chemo-surveillance has not yet been fatally damaged, whereas the majority of advanced cancer patients whose chemo-surveillance has been fatally damaged cannot be saved by such therapies [4]. That is why cancer mortality remains so high.

“Cancer is caused by wound unhealing due to the collapse of chemo-surveillance, which is an allosteric regulation the nature created to ensure perfection of wound healing” [5-9]. The human body produces metabolites active as 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 [5, 10, 11]. “DIs and DHIs function as allosteric regulators to destabilize abnormal MEs to achieve induction of terminal differentiation of PSCs, which is a critical mechanism of wound healing” [12]. Chemo-surveillance was our creation to describe the surveillance role of DIs and DHIs to eliminate cells with abnormal MEs [5]. Cancer development and wound healing are remarkably similar. Carcinogen or wound initiates the damage to trigger a cascade of responses to cause the replication and the terminal differentiation of PSCs in order to heal the wound. MEs are at the centre of these events, which play an essential role in regulating the replication and differentiation of PSCs [9]. The functionality of chemo-surveillance dictates the success of wound healing to avoid disastrous consequences of wound unhealing. Wound healing is a simple matter that comes naturally without having to put up any effort, because of the functioning of chemo-surveillance. Cancer therapy should also be a simple matter if the functionality of chemo-surveillance can be restored to that of healthy people [13-15]. “Cell differentiation agent (CDA) formulations are preparations made up by DIs and DHIs that can quickly replenish the depleted CDA of cancer patients to help control the build-up of cells with abnormal MEs. Evidently, CDA formulations are the best drugs to eliminate PSCs and CSCs, since these drugs are the partners of these cells to carry out their biological mission of wound healing. The elimination of CSCs is far more important than the elimination of CCs to account for the success of cancer therapy since most fatal effects of cancer are the making of CSCs such as metastasis, recurrence, drug resistance and angiogenesis” [16-18].

2. COMMENTARIES AND DISCUSSIONS

2.1 Abnormal MEs as the Most Critical Issue of Cancer

“Perpetual proliferation is the most outstanding feature of cancer. The blockade of differentiation the activation of oncogenes and/or the inactivation of suppressor genes are responsible for the perpetual proliferation of cancer cells. The blockade of differentiation is caused by abnormal MEs which is the most critical issue of cancer but attracts very little attention. Abnormal MEs are due to the association of MEs with telomerase” [19], which happens on PSCs, the precursors of CSCs in the preneoplastic state, and carries on to CSCs and CCs, whereas oncogenes and suppressors genes emerge quite late in the cancer development. Abnormal MEs are a single event shared by all cancers [20], **whereas oncogenes and suppressor genes involved in the pathogenesis of different cancers are multiple**. A stroke to eliminate abnormal MEs can cure all cancers, **including** the elimination of chromosomal abnormalities [9, 13, 16-18, 21-31], whereas the correction of a particular gene abnormality can only slow down the replication of cancer cells displaying such specific abnormality. One chromosomal abnormality may be solved to slow down the replication of cancer cells for a while, but there may soon pop up another chromosomal abnormality to negate the therapeutic effect achieved. The development of unresponsiveness is common in targeted therapies [30]. Therapy to target abnormal MEs can offer a permanent cure because cancer cells all become terminally differentiated cells unable to recover the ability to replicate. Obviously, abnormal MEs are the most critical issue of cancer [31]. Therapies based on the killing of CCs do not have to take into consideration what is more important to contribute to the development of cancer. Killing of CCs can wipe out all issues involved. The problems of cancer therapies based on the killing of CCs are the contribution to damage chemo-surveillance and the inability to take out CSCs which are protected by drug resistance and anti-apoptosis mechanisms [14, 15, 29].

Why are abnormal MEs the most critical issue of cancer? Because MEs play an essential role in the regulation of cell replication and differentiation cancer arises as a consequence of cell differentiation becoming faulty. Because of its important biological role in the regulation of cell replication and differentiation, MEs are subject to exceptional allosteric regulations [9,31]. Allosteric regulation is an important biological regulatory mechanism for the maintenance of biological optimum to avoid extreme often to display clinical symptoms. The most important enzymes involved in the regulation of biological processes are subject to allosteric regulation. MEs are exceptionally subject to double allosteric regulations, one on the individual enzymes and another on the enzyme complex. MEs are essential for the regulation of cell replication and differentiation by virtue of the fact that DNA methylation controls the expression of tissue-specific genes [32], and pre-rRNA methylation controls the production of the ribosome [33], which in turn dictates the commitment of a cell to initiate cell replication [34]. If enhanced production of ribosomes is locked in place, it becomes a factor to drives carcinogenesis [35]. MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH) [36]. On the individual enzymes, SAHH is the receptor of steroid hormones or related allosteric regulators. SAHH is an unstable enzyme which requires a stabilizing factor such as steroid hormone or related allosteric regulators to assume a stable configuration to form a dimeric enzyme complex with MT and this dimeric enzyme complex is then in a position to form a ternary enzyme complex with MAT. Steroid hormone or related allosteric regulators dictate the optimum of cell growth

and function. In telomerase-expressing cells, MEs are associated with telomerase [19]. The association of MEs with telomerase changes the kinetic properties of the MAT-SAHH isozyme pair and the regulation to tilt in favour of cell replication. K_m values of the telomerase-associated isozyme pair are 7-fold higher than the normal isozyme pair. The increased K_m values are an indication that cells with abnormal MEs have larger pool sizes of S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine (AdoHcy). A larger pool size of AdoMet and AdoHcy is important for the promotion of the growth of cells with abnormal MEs. It has been shown by Prudova et al. [37] that AdoMet could protect the protein from protease digestion. Chiba et al. [38] found that pool sizes of AdoMet and AdoHcy shrunk greatly when HL-60 cells were induced to undergo terminal differentiation. Obviously, abnormal MEs play an important role in the build-up of cells with abnormal MEs. Abnormal MEs do not seem to cause problems for normal stem cells such as embryonic stem cells (ESCs) and PSCs which express telomerase. There are safety mechanisms such as contact inhibition to restrict the build-up of normal stem cells with abnormal MEs, TET-1 enzyme to bypass the blockade of differentiation by abnormal MEs [23, 24] and chemo-surveillance to destabilize abnormal MEs [5-7]. Problems may arise when these safety mechanisms become dysfunctional to display clinical symptoms such as tissue fibrosis, dementia, organ failure and cancer [8, 14, 15, 39]. The protection of chemo-surveillance is particularly important to avoid the disastrous consequences of wound unhealing.

2.2 Chemo-surveillance as an Allosteric Regulation to Avoid Pathological Build-up of Cells with Abnormal MEs

Wound healing is an extremely important biological issue, so that the mature creates chemo-surveillance as an allosteric regulation to ensure perfection of wound healing to avoid pathological build-up of cells with abnormal MEs. Because of nature's creation of chemo-surveillance, wounds are always healed without having to put up any effort. Take surgical wounds, for example, treatments with sutures and antibiotics are subsidiary to speed up and to prevent infection. So, wound healing really is a simple matter. Cancer arises due to the failure to heal wounds [40]. When an animal was challenged with a hepatocarcinogen, the host liver was actively engaged in the repair of damages created by the hepatocarcinogen manifested as numerous tiny preneoplastic hyperplastic nodules which display abnormal MEs. These nodules must represent an active proliferation of PSCs in the process of wound healing. Most of these preneoplastic hyperplastic nodules disappeared, suggesting completion of wound healing. Only a few larger-sized carcinomas appeared later, obviously from unhealed tiny hyperplastic nodules. If the animal was given Antineoplaston A10 during the challenge with hepatocarcinogen, the hepatocarcinogenesis process could be effectively prevented [42]. Antineoplaston A10 is phenylacetylglutamine which was effective as an anti-cachexia agent to reverse the excessive urinary excretion of low molecular weight metabolites often associated with cancer patients [5]. It appears that the protection of the functionality of chemo-surveillance is good enough to ensure the completion of wound healing created by hepatocarcinogen to prevent carcinogenesis. The administration of Antineoplaston A10 alone was also effective in curing early-stage cancer [5]. The effectiveness of Antineoplaston A10 in the chemoprevention of carcinogenesis and in the therapy of cancer is attributable to its effect

to protect and restore the functionality of chemo-surveillance. Antineoplaston A10 was ineffective in affecting the growth of cancer cells even at very high concentrations. The effective chemicals are metabolites of wound healing produced by animals or the human body.

We knew that the human body generated metabolites with DIs and DHIs [5, 10, 11]. DIs and DHIs are hydrophobic metabolites that can be retained by C18 and recovered by 80% methanol. Peptides share the chemical properties of DIs and DHIs. Therefore, peptides can serve as surrogate molecules to represent DIs and DHIs content of the plasma and urine. Quantitative assays of plasma and urinary peptide, based on peptide/ml plasma over peptide/mg creatinine, revealed that healthy people could maintain a steady plasma/urine ratio of around 0.8.

Assigning the plasma/urine peptide ratio around 0.8 as the cell differentiation agent (CDA) with a level of 5. The distribution of 108 cancer patients in percentages among CDA levels of 5:4:3:2:1:0.5 were 1.8:6.5:16.7:35.2:22.2:19.6 [43]. CDA levels reflect the status of cancer patients very well. The higher the level the healthier the patients. Evidently, the progression of the disease causes CDA levels to drop, and the administration of cytotoxic drugs accelerates the decline of CDA levels. CDA at level 3 is probably the critical level to determine the effectiveness of therapies with cytotoxic agents. Above CDA3, cancer patients may have the chance to restore chemo-surveillance to subdue surviving CSCs, whereas below CDA3, the chance for the restoration of chemo-surveillance to combat surviving CSCs is almost none. Cytotoxic therapies can only benefit the minority of early-stage cancer patients, whereas the majority of advanced cancer patients with CDA levels below 3 cannot benefit from cytotoxic therapies. All cancer patients can benefit from therapy with Antineoplaston, which can elevate CDA levels. Patients treated with Antineoplaston if responding well, CDA level would increase to approach that of healthy people. If not, the CDA level continued to decline [43]. Antineoplastons are preparations of natural wound-healing metabolites. Fast-growing cancers are known to express a high level of degradation enzymes to salvage starting substrates for macromolecular syntheses in order to support their fast growth. Natural wound healing metabolites may be degraded in faster-growing cancer cells to lose effectiveness. For the elimination of faster-growing CCs, it may be necessary to employ non-natural DIs and DHIs to bypass degradative enzymes. Two sets of CDA formulations may be necessary to achieve effective therapy of cancer. One set CDA-CSC is made by natural DIs and DHIs to target CSC, and another set CDA-CC is made by non-natural DIs and DHIs to target faster-growing CCs [15]. A combination therapy relying on CDA-CSC to target CSCs and cytotoxic agents or immunological agents to target CCs may also be effective for cancer therapy [27, 29]. Our studies clearly indicate that cancer is caused by the collapse of chemo-surveillance. Therefore, a top priority to save cancer patients is to restore the functionality of chemo-surveillance. When the functionality of chemo-surveillance is restored to the level of CDA5 as the healthy people, the therapy of cancer will be as easy as wound healing requiring no effort.

2.3 Screening for Suitable Cancer Drugs in Myelodysplastic Syndrome

Cancer is caused due to the failure to heal wounds [40]. Wound healing requires the proliferation and the terminal differentiation of PSCs [12]. Wound triggers biological and immunological responses [44]. The biological response involves the release of arachidonic acid

(AA) from membrane-bound phosphatidylinositol for the synthesis of prostaglandins (PGs) which are good for wound healing. Although PGs are excellent DIs [45], their function at the initial stage of the wound is believed to create edema for the extravasation of inhibitors such as DIs and DHIs in order for PSCs to proliferate. The final stage of wound healing is accomplished by chemo-surveillance, nature's creation of allosteric regulation to destabilize abnormal MEs. The immunological response of the wound prompts the production of TNF which is bad for wound healing. TNF is responsible for cachexia symptoms to cause the collapse of chemo-surveillance to heal wounds. The failure to heal wounds forces PSCs to evolve into CSCs.

The development of MDS follows exactly the wound healing course. MDS often starts with a display of an immunological disorder [46] which prompts the production of inflammatory cytokines. "Among these cytokines, TNF is the critical factor related to the development of MDS, because antibody to TNF was effective to halt the progression of MDS" [47]. "TNF 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 is also responsible for cachexia symptoms commonly shared by inflammatory patients and cancer patients. A characteristic disorder of cachexia is the excessive urinary excretion of low molecular weight metabolites because of vascular hyperpermeability caused by TNF" [48 49]. "As a consequence, chemo-surveillance normally operating in healthy people to keep cells with abnormal MEs in check becomes dysfunctional to heal wounds, thus allowing PSCs to evolve into CSCs. The propagating pathological cells have been identified as CSCs" [50]. Thus, MDS is a disease attributable entirely to CSCs.

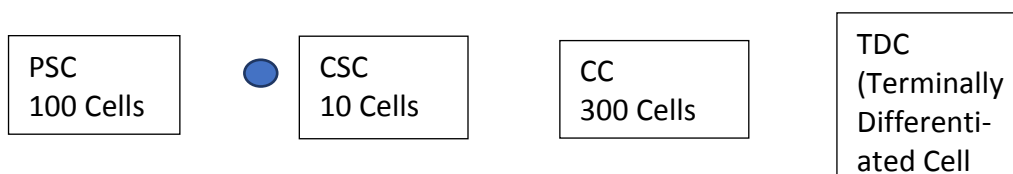
Therapy of MDS requires terminal differentiation of pathological CSCs to become functional erythrocytes which is exactly the critical mechanism of wound healing requiring the terminal differentiation of PSCs. Killing of CSCs cannot cure MDS. Besides, killing of CSCs cannot be easily done, because these cells are protected by drug resistance and anti-apoptosis mechanisms. Elimination of CSCs is very important for cancer therapy because these cells contribute to most of the fatal effects of cancer such as metastasis, recurrence, drug resistance and angiogenesis. Evidently, CDA formulations made up of DIs and DHIs are the best drugs to eliminate CSCs. So far vidaza, decitabine and CDA-2 were the three drugs approved for the therapy of MDS in China. Vidaza and decitabine were also approved for the therapy of MDS in the USA. CDA-2 was our creation which was a preparation of wound-healing metabolites purified from freshly collected urine by reverse-phase chromatography employing XAD-16 as the adsorbant [22]. CDA-2 has all wound healing elements as Antineoplastons except peptides which are not retained by XAD-16. CDA-2 inactivates abnormal MEs through DIs and DHIs as allosteric regulators, whereas vidaza and decitabine inactivate abnormal MEs through covalent bond formation between methyltransferase and 5-azacytosine base incorporated into DNA from vidaza or decitabine[51]. According to Professor Jun Ma, Director of Harbin Institute of Hematology and Oncology who was instrumental in conducting clinical trials for the approval of the three MDS drugs in China, findings based on two cycles of clinical trial protocol each cycle of 14 days, showed CDA-2 had a slightly better therapeutic efficacy based on cytological evaluation, and a marked better therapeutic efficacy based on hematological improvement evaluation, meaning patients were no longer dependent on blood transfusion to stay healthy

[52]. Better yet, CDA-2 was devoid of severe adverse effects, whereas vidaza and decitabine were known carcinogens [53, 54] and very toxic to DNA [55-57]. Obviously, CDA-2 is the drug of choice for the therapy of MDS with better therapeutic efficacy and devoid of adverse effects. CDA-2, vidaza and decitabine are the three drugs to pass the Litmus test of MDS as the right cancer drugs. Most drugs approved for cancer therapy cannot pass the Litmus test of MDS as the right cancer drugs. Evidently, the elimination of CSCs is the most important criterion for the effective therapy of cancer. Drugs to inactivate abnormal MEs are the best drugs to eliminate CSCs. Destabilization of abnormal MEs through DIs and DHIs as nature's creation of allosteric regulation is the best approach to cancer therapy.

2.4 Restoration of Chemo-surveillance as a Top Priority to Save Cancer Patients

The concept of cancer as wound unhealing was first introduced by the great German scientist Virchow in the 19th century [58]. It was again brought up by Dvorak in 1986 [59]. The close relationship between cancer and wound healing was noticed by MacCarthy-Morrhough and Martin [60]. We provided the most important details on this subject that included abnormal MEs to block differentiation [19, 20, 61]; chemo-surveillance as the nature's creation of allosteric regulation to ensure perfection of wound healing [3, 5-8]; DIs and DHIs as wound healing metabolites and also as active players of chemo-surveillance [10, 11]; hypomethylation of nucleic acids as the most critical mechanism for the induction of terminal differentiation of cells with abnormal MEs [62]; the mechanism of wound healing to involve the proliferation and the terminal differentiation of PSCs [3, 12, 15, 40]; and the evolution of CSCs from PSCs due to wound unhealing [23, 24, 63, 64]. These studies very convincingly establish that cancer arises as a consequence of wound unhealing, and the most critical event is the collapse of chemo-surveillance. Thus, the restoration of chemo-surveillance is a top priority to save cancer patients. Chemo-surveillance is nature's creation to prevent the pathological build-up of cells with abnormal MEs. It is the most effective strategy to eliminate CSCs, the most troubling elements of cancer cells to contribute to the fatal effects of cancer. The contribution to cause the damage to chemo-surveillance and the ineffectiveness of CSCs are responsible for the failure of cytotoxic agents to put cancer away [2, 4, 8, 13-18, 23, 24, 65]. Once CSCs can be effectively under control by restoring CDA to the healthy level 5 of healthy people, curing cancer can be as easy as healing a wound. Elimination of CCs is, of course, an important issue of cancer. After all, CCs constitute the major part of cancer mass. But Elimination of CCs cannot bring down cancer mortality [1]. Elimination of CSCs can bring down cancer mortality. The most important matter is to approve CDA formulations to restore chemo-surveillance to put away problems contributed by CSCs. Approval of CDA formulations takes 10 years of clinical trials. It will be 10 years before we can begin to see the drop in cancer mortality if cancer establishments are willing to accept CDDA formulations as the right cancer drugs.

A summary drawing to show the restoration of chemo-surveillance through CDA formulations to save cancer patients vs cytotoxic agents to cause cancer mortality is presented in the following Figure-1.



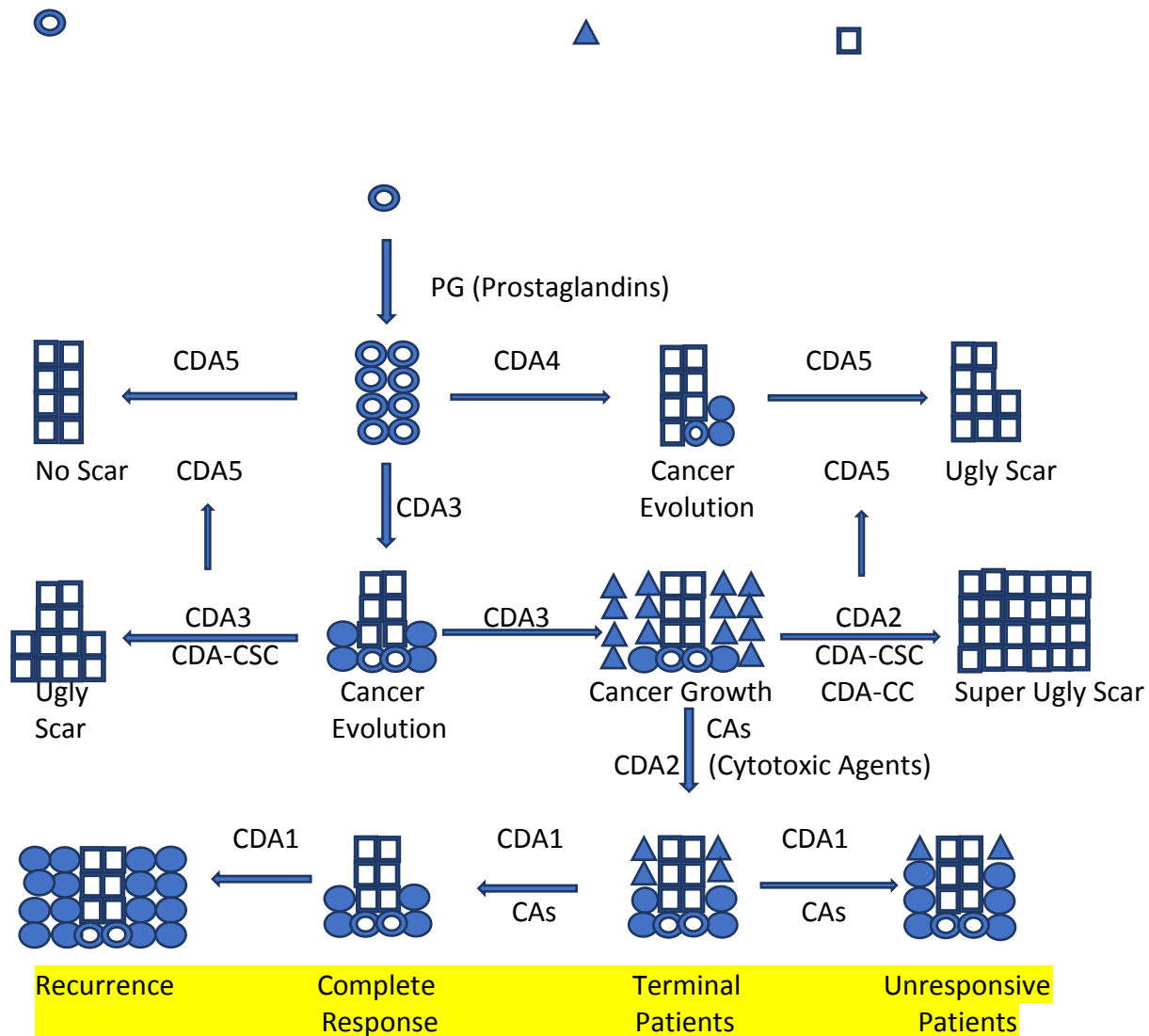


Figure 1. Restoration of chemo-surveillance through CDA formulations to save cancer patients vs cytotoxic agents to cause cancer fatality.

CDA5 depicts chemo-surveillance at the level of health people, and CDA4-1 depict it at lower levels due to the collapse of chemo-surveillance. CAs include cytotoxic chemotherapeutic agents, radiation, apoptosis-inducing agents and immunological therapeutic agents. The progression of cancer is a factor to causes the collapse of chemo-surveillance, and the application of cytotoxic agents accelerates the collapse of chemo-surveillance. CDA-CSC is a CDA formulation made up of natural DI+DHI such as ED₅₀ of arachidonic acid+2xRI_{0.5} of pregnenolone and CDA-CC is a CDA formulation made up of unnatural DI+DHI such as ED₅₀ of BIBR 1532+2xRI_{0.5} of pyrvinium pamoate [15]. Administration of CDA formulations can restore chemo-surveillance to assist cancer therapy no matter how badly chemo-surveillance has been damaged. Cytotoxic agents contribute to the damage of chemo-surveillance. Only early-stage cancer patients whose chemo-surveillance has not yet been fatally damaged can benefit from

cytotoxic therapy, relying on the restoration of chemo-surveillance to subdue surviving CSCs which are not responsive to cytotoxic agents. Advanced cancer patients whose chemo-surveillance has been fatally damaged become unresponsive or fortunately still responsive to reach a complete response are ultimately succumb to recurrence.

3. CONCLUSION

Cancer is caused by wound unhealing due to the collapse of chemo-surveillance, which is nature's creation of allosteric regulation to prevent the pathological build-up of cells with abnormal MEs. MEs play an important role in cell replication and differentiation. Because of this important biological role, MEs are subject to exceptional **double allosteric regulations**, one on the individual enzymes and another on the enzyme complex. MEs are a ternary enzyme complex consisting of MAT-MT-SAHH. On individual enzymes, SAHH is the receptor of steroid hormones or related allosteric regulators which dictate the optimum of growth and differentiation. In telomerase-expressing cells, MEs are subject to another allosteric regulation involving telomerase and chemo-surveillance. Telomerase tilts the regulation in favour of cell growth. Cell growth is an important mechanism for the development of the fetus and wound healing because ESCs and PSCs express telomerase. There are safety mechanisms to limit the build-up of normal stem cells such as contact inhibition, TET-1 enzyme to undergo lineage transitions and chemo-surveillance to keep abnormal MEs under control. When such safety mechanisms become dysfunctional, PSCs are forced to evolve into CSCs and then progress to faster-growing CCs, which are an effort to heal the wound. Obviously, chemo-surveillance plays a very important role in limiting the build-up of cells with abnormal MEs, the restoration of this important mechanism is most important to save cancer patients.

REFERENCES

1. Google search on cancer statistics-NCI and American Cancer Society.
2. Liao MC, Fruehauf JP. It has been half a century since President Nixon declared war on cancer: Destabilization of abnormal methylation enzymes has the blessing of the nature to win the war on cancer. *Adv Complement Alt Med*. 2020; 6(1): 538-539.
3. Liao MC, Craig CL. Wound healing metabolites to heal cancer and unhealed wounds. *Intl Res J Oncol*. 2022; 6(3): 8-20.
4. Liao MC, Craig CL, Baker LL. CDA formulations to fulfill cancer moonshot and to win the war on cancer. *Int J Res Oncol*. 2023; 2(2): 1-8.

5. Liao MC, Szopa M, Burzynski B, Burzynski SR. Chemo-surveillance: A novel concept of the natural defense mechanism against cancer. *Drugs Exptl Clin Res.* 1989; 13(Suppl. 1): 72-82.
6. Liao MC, Baker LL. The functionality of chemo-surveillance dictates the success of wound healing as well as cancer therapy. *Nov Res Sci.* 2021; 7(2): 1-3.
7. Liao MC, Craig CL. Chemo-surveillance as a natural mechanism to ensure perfection of wound healing to avoid cancer evolution and to cure cancer. In: *New Horizons in Medicine and Medical Research.* 2022; Vol 6, Chapter 3. Print ISBN: 978-93-5547-4.
8. Liao MC, Craig CL, Baker LL. Wound unhealing as a grave issue of cancer. *Intl Res J Oncol.* 2023; 6(1): 97-103.
9. Liao MC, Craig CL, Liao LL. Abnormal methylation enzymes as the most critical issue of cancer. *Intl Res J Oncol.* 2023; 6(2): 168-176.
10. Liao MC, Lee SS, Burzynski SR. Modulation of cancer methylation complex isozymes as a decisive factor in the induction of terminal differentiation mediated by Antineoplaston A5. *Intl J Tiss React.* 1990; 12(Suppl.): 17-36.
11. Liao MC, Liao CP, Burzynski SR. Potentiation of induced terminal differentiation by phenylacetic acid and related chemicals. *Intl J Exptl Clin Chemother.* 1992; 5: 9-17.
12. Liao MC, Craig CL. On the mechanism of wound healing and the impact of wound on cancer evolution and cancer therapy. *Intl Res J Oncol.* 2021; 5(3): 25-31.
13. Liao MC, Fruehauf JP. Restoration of the chemo-surveillance capability is essential for the success of chemotherapy and radiotherapy to put cancer away. *Adv Complement Alt Med.* 2019; 5(4): 474-475.
14. Liao MC, Baker LL. Destruction promotes the proliferation of progenitor stem cells and cancer stem cells. Therefore, non-destruction is a better strategy for cancer therapy. *J Pharmacol Pharmaceu Pharmacovigi.* 2020; 4: 029. DOI: 10.24966/PPP-5649/100029.
15. Liao MC, Craig CL, Baker LL. Wound healing process as the most appropriate modality of cancer therapy. *Eur J Applied Sci.* 2023; 11(1): 463-471.
16. Liao MC, Fruehauf JP. The winner of the contest to eradicate cancer stem cells wins the contest of cancer therapies: The winner is cell differentiation agent formulations. *Adv Complement Alt Med.* 2020; 5(4): 476-478.
17. Liao MC, Fruehauf PA, Zheng JH, Fruehauf JP. Development of synthetic cell differentiation agent formulations for the prevention and therapy of cancer via targeting of cancer stem cells. *Cancer Stu Ther J.* 2019; 4(1): 1-15.
18. Liao MC, Baker LL. Eradication of cancer stem cells to win the war on cancer. *Nov Res Sci.* 2021; 6(5): 1-3.
19. Liao MC, Zhuang P, Chiou GCY. Identification of the tumor factor of abnormal methylation enzymes as the catalytic subunit of telomerase. *Clin Oncol Cancer Res.* 2010; 7(2): 86-96.

20. Liao MC, Chang CF, Giovannella BC. Demonstration of an altered S-adenosylmethionine synthetase in human malignant tumors xenografted into athymic nude mice. *J Natl Cancer Inst.* 1980; 64(5): 1071-1075.
21. Liao MC. Abnormal methylation enzymes: A selective molecular target for differentiation therapy of cancer. *Chin Pharm J.* 2004; 56(2): 57-67.
22. Liao MC. Pharmaceutical composition inducing cancer cell differentiation and the use for treatment and prevention of cancer. US Patent 7232578.B2, 2007.
23. Liao MC, Kim JH, Fruehauf JP. Destabilization of abnormal methylation enzymes: Nature's way to eradicate cancer stem cells. *Online J Complement Alt Med.* DOI: 10.33552/OJCAM.2019.02.000456.
24. Liao MC, Kim JH, Fruehauf JP. Destabilization of abnormal methylation enzymes to combat cancer: The nature's choice to win the war on cancer. Lambert Academic Publishing. 2020; 978-620-2-65889-7.
25. Liao MC, Fruehauf PA, Zheng ZH, Fruehauf JP. Destabilization of abnormal methylation enzymes as an effective therapeutic strategy via induction of terminal differentiation to take out both cancer stem cells and cancer cells. In: *Current Aspects in Pharmaceutical Research and Development.* 2021; Vol. 2, Chapter 11: 120-142. Print ISBN 978-93-5547-055-3. DOI: 10.9734-bpi/caprd/v2/13544D.
26. Liao MC, Baker LL. Eradication of cancer stem cells to win the war on cancer. *Nov Res Sci.* 2022; 6(5): 1-3.
27. Liao MC, Fruehauf JP. Winning formulas to fulfill cancer moonshot. *Intl J Res Oncol.* 2022; 1(1): 1-5.
28. Liao MC, Fruehauf JP. Cancer moonshot : Moonshot as a magic code to guide successful solutions of tough challenges such as cancer. 2023; *Intl J Res Oncol.* 2(1): 1-5.
29. Liao MC, Craig CL, Baker LL. CDA formulations to fulfill cancer moonshot and to win the war on cancer. *Int J Res Oncol.* 2023; 2(2): 1-8.
30. Liao MC, Baker LL. Abnormal methylation enzymes as the bullseye of targeted cancer therapy. *Nov Res Sci.* 2021; 7(4): 1-3.
31. Liao MC, Craig CL, Baker LL. Exceptional allosteric regulation of methylation enzymes. In: Saraydin Su (edi) : *Novel Research Aspects in Medicine and Medical Science.* 2023; Vol 4: 39-56.
32. Racanelli AC, Turner FB, Xie LY, Taylor SM, Moran RG. A mouse gene that coordinate epigenetic controls and transcriptional interference to achieve tissue specific expression. *Mol Cell Biol.* 2008; 28(2): 836-848.
33. Liao MC, Hunt ME, Hurlbert RB. Role of ribosomal RNA methylases in the regulation of ribosome production. *Biochemistry.* 1976; 15(14): 3158-3164.
34. Bernstein KA, Bleichert F, Bean JM, Cross FR, Baserga SJ. Ribosome biogenesis is sensed at the start cell cycle check point. *Mol Biol Cell.* 2007; 18(3): 953-964.
35. Justilien Y, Ali SA, Jamieson L, Yin N, Cox AD, Der CJ, et al. Ect2-dependent rRNA synthesis is required for KRAS-TRP53-driven lung adenocarcinoma. *Cancer Cell.* 2017; 31(2): 256-269.

36. Liau MC, Chang CF, Saunders GS, Tsai YH. S-Adenosylhomocysteine hydrolases as the primary target enzymes in androgen regulation of methylation complexes. *Arch Biochem Biophys.* 1981; 208(1): 261-272.
37. Prudova A, Bauman Z, Braun A, Vitvitsky V, Lu SC, Banerjee R. S-Adenosylmethionine stabilizes cystathionine beta-synthase and modulates redox capacity. *Proc Natl Acad Sci USA.* 2006; 103(17): 6489-6494.
38. Chiba P, Wallner C, Kaizer E. S-Adenosylmethionine metabolism in HL-60 cells: Effect of cell cycle and differentiation. *Biochim Biophys Acta.* 1988; 971(1): 38-45.
39. Liau MC, Baker LL. The impact of COVID-19 pandemic on cancer patients. *Intl Res J Oncol.* 2022; 6(1): 97-103.
40. Liau MC, Craig CL. No scar as an indication of perfect wound healing, ugly scar as imperfect wound healing and cancer as failed wound healing. *J Cancer Tomor Intl.* 2022; 12(1): 29-34.
41. Liau MC, Chang CF, Becker FF. Alteration of S-adenosylmethionine synthetases during chemical hepatocarcinogenesis and in resulting carcinomas. *Cancer Res.* 1979; 39: 2113-2119.
42. Kamparath BN, Liau MC, Burzynski B, Burzynski SR. Protective effect of Antineoplaston A10 in hepatocarcinogenesis induced by aflatoxin B1. *Intl J Tiss React.* 1990; 12(Suppl.): 43-50.
43. Liau MC, Szopa M, Burzynski B, Burzynski SR. Quantitative assay of plasma and urinary peptides as an aid for the evaluation of patients undergoing Antineoplaston therapy. *Drugs Exptl Clin Res.* 1987; 13(Suppl.): 61-70.
44. Ho ATV, Palla AR, Blake MR, Yual ND, Wang YX, Magmusson KEG, et al. Prostaglandin E2 is essential for efficacious skeletal muscle stem function, augmenting regeneration and strength. *Proc Natl Acad Sci USA.* 2017; 114(26): 6675-6684.
45. Liau MC, Kim JH, Fruehauf JP. Arachidonic acid and its metabolites as the surveillance differentiation inducers to protect healthy people from becoming cancer patients. *Clin Pharmacol Toxicol Res.* 2021; 4(1): 7-10.
46. Williamson PJ, Kruger AR, Reynolds PJ, Hamlin TJ, Oscier DG. Establishing the incidence of myelodysplastic syndromes. *Br J Haemato.* 1994; 87(4): 743-745.
47. Boula A, Vouglarelis M, Giannouli S, Katrinakis G, Psyllaki M, Pontikoglou C, et al. Effect of CA2 of antitumor necrosis factor-alpha antibody therapy on hematopoiesis of patients with myelodysplastic syndromes. *Clin Cancer Res.* 2006; 12(10): 3099-3108.
48. Itkin T, Rafii S. Leukemia cells "gas up" leaky bone marrow blood vessels. *Cancer Cell.* 2017; 32(3): 276-278.
49. Passaro D, Di Tullio A, Abarrategi A, Rousault-Pierre K, Foster K, Ariza-McNaughton L, et al. Increased vascular permeability in the bone marrow microenvironment contributes to disease progression and drug response in acute myeloid leukemia. *Cancer Cell* 2017; 32(3): 324-341.

50. Woll PS, Kjallquist U, Chowdhury O, Doolittle H, Wedge DC, Thongjuea S, et al. Myelodysplastic syndromes are propagated by rare and distinct human cancer stem cells in vivo. *Cancer Cell*. 2014; 25(6): 794-808.
51. Santi DV, Norment A, Garrett CE. Covalent bond formation between a DNA-cytosine methyltransferase of DNA containing 5-azacytosine. *Proc Natl Acad Sci USA*. 1984; 81(22): 6993-6997.
52. Ma J. Differentiation therapy of malignant tumor and leukemia. *CSCO Treaties on the education of clinical oncology*. 2007; pp. 480-486.
53. Prassana P, Shack S, Wilson VL, Samid D. Phenylacetate in chemoprevention of 5-aza-2'-deoxycytidine-induced carcinogenesis. *Clin Cancer Res*. 1995; 1(18): 865-871.
54. Gaudet F, Hodgson JG, Eden A, Jackson-Grusby L, Dausman J, Gray JW, et al. Induction of tumor in mice by genomic hypomethylation. *Science*. 2003; 300(5618): 489-492.
55. Pali SS, van Emburgh BO, Sannkpal UT, Brown KD, Robertson KD. DNA methylation inhibitor 5-aza-2'-deoxycytidine induces reversible DNA damage that is distinctly influenced by DNA-methyltransferase 1 and 3B. *Mol Cell Biol*. 2008; 28(2): 752-771.
56. Kizietepe T, Hideshima T, Catley L, Raje N, Yasui H, Shiraishi N, et al. 5-Azacytidine, a methyltransferase inhibitor, induces ATR-mediated DNA-double strand break responses, apoptosis and synergistic cytotoxicity with doxorubicine and bortezomib against multiple myeloma cells. *Mol Cancer Ther*. 2007; 6(6): 1718-1727.
57. Yang Q, Wu F, Wang F, Cai K, Zhang Y, Sun Q, et al. Impact of DNA methyltransferase inhibitor, 5-azacytidine on cardiac development of zebrafish in vivo and cardiomyocyte proliferation, apoptosis, and the homeostasis of gene expression in vitro. *J Cell Biochem*. 2019; 120(10): 17479-17471.
58. Virchow R. *Die Cellular Pathologie in Ihrer Begründung auf Physiologische und Pathologische Gewebelehre*. Hirschwald. 1858: 16: 400.
59. Dvorak HF. Tumors: Wounds that do not heal. *N Engl J Med*. 1986; 315(26): 1650-1659.
60. MacCarthy-Morrrough L, Martin P. The hallmarks of cancer are also the hallmarks of wound healing. *Science Signaling*. 2020; 13: 648.
61. Liau MC, Lin GW, Hurlbert RB. Partial purification and characterization of tumor and liver S-Adenosylmethionine synthetases. *Cancer Res*. 1977; 37(2): 427-435.
62. Liau MC, Lee SS, Burzynski SR. Hypomethylation of nucleic acids: A key to the induction of terminal differentiation. *Intl J Exptl Clin Chemother*. 1989; 2: 187-199.
63. Kudo Y, Tateishi K, Yamamoto K, Yamamoto S, Asaoka Y, Ijichi H, et al. Loss of 5-hydroxymethylcytosine is accompanied with malignant cellular transformation *Cancer Sci*. 2012; 103(4): 670-676.
64. Ficzc GM, Gibben JG, Loss of 5-hydroxymethylcytosine in cancer: Cause or consequence? *Genomics*. 2011; 104(5): 352-357.

65. Liau MC, Baker LL. Cancer patients' lives matter. *Adv Complement Alt Med.* 2021; 6(5): 638-640.