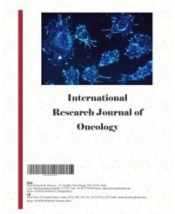

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Wound Healing, Evolution of Cancer and War on Cancer

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Authors' contributions

This work was carried out in collaboration between both authors. Author MCL designed the study, wrote the protocol and wrote the first draft of the manuscript. Author LLB managed the analyses of the study. Both authors read and approved the final manuscript.

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ABSTRACT

This review highlights wound healing, evolution of cancer, and war on cancer. Wound healing requires the proliferation and the terminal differentiation (TD) of progenitor stem cells (PSCs), which are the precursors of cancer stem cells (CSCs).Healing wound is not a big deal. If the functionality of chemo-surveillance is intact such as healthy people who can maintain a steady level of wound healing metabolites functioning as differentiation inducers (DIs) and differentiation helper inducers (DHIs).Wounds are always successfully healed without having to put up any effort, just to let the nature to do the healing. Medications such as suture and antibiotics are subsidiary to speed up the healing or to prevent infection. Acute wound affects the functionality of chemo-surveillance only temporarily, which is quickly recovered to return to the normal state. It is the chronic wound such as persistent infectious diseases or exposure to toxic chemicals including carcinogens for a long time that produces damaging effect on the functionality of chemo-surveillance.Chronic wound prompts the production of inflammatory cytokines to cause excessive urinary excretion of wound healing metabolites to affect wound healing. Without sufficient wound healing metabolites to terminate the proliferation of PCSs, it is very easy for PSCs to evolve into CSCs. It takes only a single hit to silence TET-1 enzyme to complete the transition, which is well within the reach of PSCs equipped with abnormally active methylation enzymes (MEs).CSCs can then progress to faster growing cancer cells by the activation of oncogenes or the inactivation of suppressor genes. These are exactly the processes that lead to myelodysplastic syndrome (MDS) and acute myeloid leukemia

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(AML). Cancer due to wound not healing properly is not unique to MDS and AML. It is rather a common phenomenon. War on cancer can be easily won if the battle is conducted following the nature's course to heal the wound, just like the success of wound healing without having to put up any effort in healthy people. Therefore, the best strategy to win the war on cancer is to restore the functionality of chemo-surveillance by the employment of DIs and DHIs and to prevent the loss of wound healing metabolites through anti-cachexia chemicals such as phenylacetylglutamine. Then the nature will take its course to stop the proliferation of cells with abnormal MEs that include CSCs, PSCs, and all cancer cells. Destruction strategy to kill cancer cells is definitely counter indication. It creates more damages to the functionality of chemo-surveillance to stop the growth of cells with abnormal MEs. Inability of destruction strategy to put away CSCs is a deciding factor to deny the success of destruction strategy to win the war on cancer.

Keywords: Wound healing; Change to; evolution of cancer; war on cancer; chemo-surveillance; abnormal methylation enzymes; differentiation inducers; differentiation helper inducers.

1. INTRODUCTION

Wound healing is closely related to the evolution of cancer [1-2], because wound healing requires the proliferation and the TD of PSCs, and the evolution of cancer is due to the transition of PSCs to become CSCs. Therefore, if wound is successfully healed, then the transition of PSCs to CSCs scan be avoid. But if wound is not successfully healed, then the transition of PSCs to CSCs is a very likely possibility. This review examines the issues involved in wound healing and the evolution of cancer. Wound healing is not a big deal. Wounds are always successfully healed without having to put up any effort in healthy people. We can also rely on the same successful wound healing processes to avoid cancer and to win the war on cancer. On the other hand, wounds may not be healed under pathological conditions that result in the loss of wound healing metabolites. Likewise, without the help of wound healing metabolites, cancer cannot be put away. Destruction strategy of cancer therapy is following the course that fails to heal the wound, which can never be able to win the war on cancer.

2. WOUND HEALING

PSCs and CSCs are very much alike on cell features and biological missions. It is very likely that CSCs are originated from PSCs. In the transition, TET-1 enzyme is silenced, which marks the critical difference between PSCs and CSCs [3-4]. PSCs are still able to carry out differentiation programs, relying on TET-1 enzyme to achieve DNA hypomethylation required for the cell to undergo TD [5]. The differentiation capability of CSCs and cancer cells is completely blocked. PSCs are the most primitive cells to give rise to the organs or tissues during embryonic development of the fetus. A small portion of these primitive cells are retained in the organs or tissues to meet the need of expansion or the repair of damage. PSCs and CSCs express ATP binding cassette pumps that can effectively exclude toxic chemicals [6], and have anti-apoptosis programs that can negate apoptosis signals activated by DNA damaging radiation [7]. PSCs and CSCs normally reside dormantly in acidic and hypoxic microenvironment hard to reach by the blood. PSCs and CSCs express chemotactic receptors, thus sensitive to signals calling for the expansion or repair. MEs of PSCs are abnormal like cancer cells due to the association with telomerase [8], making differentiation hard to proceed. Hindrance of differentiation may be a critical mechanism to buildup cell mass for PSCs and CSCs to repair the wound. The proliferation and the TD of PSCs are the most important biological processes for wound healing. Since we do not know how to handle these biological processes, we let the nature to take its course to heal the wound. Wound incites biological response and immunological response. The biological response involves the breakdown of membrane bound phospholipid to release arachidonic acid (AA) for the synthesis of prostaglandins (PGs) [1], which are active DIs good for wound healing to terminate the proliferation of PSCs [9]. Inability to terminate the proliferation of PSCs always runs a risk for PSCs to evolve into CSCs simply by a single hit to silence TET-1 enzyme, which is well within the reach of PSCs equipped with abnormal MEs, and then to progress to faster growing cancer cells by the activation of oncogenes or the inactivation of suppressor genes. The immunological response prompts the production of inflammatory cytokines which are bad for wound healing. Among these cytokines,

tumor necrosis factor (TNF) is the most damaging [10]. TNF causes the apoptosis of unipotent stem cells on one hand, and causes the symptom of cachexia on the other hand to result in the collapse of chemo-surveillance, which is a natural defense mechanism to prevent the buildup of cells with abnormal MEs such as PSCs and cancer cells [11]. The metabolites responsible for chemo-surveillance are the metabolites involved in wound healing [9,12]. Therefore, the perfection of wound healing is the natural defense mechanism to avoid cancer [13].

Healing wound is not a big deal. Wounds are always successfully healed without having to put up any effort, just to let the nature to do the healing. Medications such as suture and antibiotics are subsidiary to speed up the healing or to prevent infection. If chemo-surveillance is intact such as healthy people who can maintain a steady level of wound healing metabolites functioning as DIs and DHIs [11,12], then a spike of PGs produced in response to wound can promote perfect wound healing to avoid cancer. Chemo-surveillance metabolites are made up by DIs and DHIs. DIs are chemicals that can eliminate telomerase from abnormal MEs and DHIs are chemicals inhibitory to the enzymes of ternary MEs consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)- S-adenosylhomocysteine hydrolase (SAHH) [14]. SAHH is a steroid hormone receptor, very responsive to steroid hormones and other growth factors. MEs of cells expressing telomerase such as PSCs and cancer cells are abnormal due to the association with telomerase as above described [8]. The abnormal MAT-SAHH isozyme pair display K_m values 7-fold higher than the normal isozyme pair [8,14]. The higher $K_m$values enable cancer cells to maintain larger pool sizes of S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine (AdoHcy), which are the reasons why abnormal MEs are exceptionally stable because AdoMet can protect protein against protease digestion [15]. Stable and active MEs are essential for the promotion of malignant growth. It has been shown by Chiba et al. [16] that the pool sizes of AdoMet and AdoHcy shrunk greatly when cancer cells were induced to undergo TD. Thus, destabilization of abnormal MEs is a critical mechanism to terminate proliferation of cells with abnormal MEs. DIs are more important than DHIs for the induction of TD. DHIs are totally ineffective without DIs [17]. However, DHIs are also essential for the completion of the induction of TD. TD induced by DIs alone is often incomplete due to damages caused by DIs to interrupt differentiation process [9,17]. The damages are very likely due to the conversion of MTs into nucleases when ternary MEs are destabilized to dissociate into monomeric enzymes. Such damages can be prevented in the presence of DHIs to achieve completion of TD. Completion of TD is important for the therapy of cancer, because the damages to interrupt differentiation can be repaired to result in recurrence.Therefore, combination of DIs and DHIs is essential for the formulation of good cell differentiation agents (CDA).

The membrane hyperpermeability triggered by wound is a necessary evil to allow the release of DIs and DHIs, which function as a brake to prevent the proliferation of PSCs, from inside of PSCs so that PSCs can proliferate to work on the repair. Localized inflammatory response is helpful for the wound healing. The very active DIs of PGs synthesized definitely are the nature's design for the wound healing. PGs plus sufficient chemo-surveillance metabolites are good enough to heal the wound perfectly. Although inflammatory cytokines are also produced in the process, the bad effect of cytokines is usually overwhelmed by the good effect of wound healing metabolites. Therefore, when the functionality of chemo-surveillance is intact, the outcome is always perfect wound healing. But if the functionality of chemo-surveillance has been compromised due to existing pathological conditions, then the bad effect of TNF prevails to interfere TD of PSCs, so that wound cannot be healed as expected. PSCs keep on proliferating to evolve into CSCs and then to faster growing cancer cells [13].

3. CANCER ARISES AS A CONSEQUENCE OF WOUND NOT HEALING PROPERLY

Acute wound affects chemo-surveillance only temporarily, which is quickly recovered to return to the normal state. It is the chronic wound such as persistent infectious diseases or exposure to toxic chemicals including carcinogens for a long time that produces damaging effect on chemo-surveillance to affect wound healing. This is exactly the case of MDS. MDS often starts with a display of an immunological disorder [18], which prompts the production of inflammatory cytokines. Among such cytokines, TNF is the critical factor related to the development of MDS [10]. 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 is also named cachectin, because of its causation of cachexia symptom commonly shared by cancer and inflammatory patients. A characteristic disorder of cachexia is the excessive urinary excretion of low molecular weight metabolites because of vascular hyperpermeability caused by TNF [19-20]. As a consequence, chemo-surveillance normally operating in healthy people to keep PSCs in check becomes dysfunctional, allowing PSCs to buildup in order to replenish unipotent stem cells wiped out by TNF. The high level of telomerase in the peripheral and bone marrow leukocytes in MDS patients is an indication of the widespread multiplication of PSCs [21-22]. During the course of MDS progression, mutations affecting enzymes are frequently observed [23-25], which may play significant roles on the evolution of PSCs to become CSCs [26]. As anemia in MDS patients becomes worse, chromosomal abnormalities such as translocations and deletions characteristic of cancer cells arise to accelerate replication, eventually pushing MDS patients to progress to AML [27-30].

Cancer due to wound not healing properly is not unique to MDS and AML. It is rather a common phenomenon. We have previously observed that the protection of the integrity of chemo-surveillance by Antineoplaston A10, namely phenylacetylglutamine, could effectively prevent chemical carcinogenesis [31-32], and achieve effective therapy of early stage cancer [11]. These observations strongly support our hypothesis that cancer arises due to wound not healing properly [13]. We have also observed that abnormal MEs were detectable in preneoplastic hyperplastic nodules before the appearance of carcinomas during chemical hepatocarcinogenesis [33]. This was an indication that carcinomas were derived from cells expressing abnormal MEs in the preneoplastic stage, which were very likely PSCs. So the occurrence of human cancer and experimental animal cancer all suggests that cancer is originated from PSCs because of the failure of wound healing.

4. WAR ON CANCER

President Nixon declared war on cancer in 1971 [34-35]. A presidential project is either to solve a catastrophic national crisis such as the Manhattan Project of President Roosevelt to develop atomic bomb to finish World War II, or to establish a monumental national honor such as the Apollo Project of President Kennedy to send the people to the moon and back. Apparently, President Nixon considered solution of cancer a monumental national honor to declare war on cancer. It was a big challenge to the health profession. But unfortunately the health profession failed the challenge to put cancer away during the 5 years of intensive presidential support and the following 45 years of almost entire national support allocated to cancer. Destruction that includes cytotoxic chemotherapy and radiation therapy was the choice of cancer establishments to combat cancer in the past but failed to put cancer away. Destruction actually is inappropriate for the therapy of a disease arising due to wound not healing properly. It is following the course that fails to heal the wound. It creates more wounds to aggravate the already bad situation. It can kill sensitive cancer cells and stem cells, but the damages it created promote the proliferation of CSCs and PSCs to work on the repair. The end result is to replace sensitive cancer cells with tough untreatable CSCs and the buildup of PSCs to evolve into additional cancer. The transition of the tumor to one containing predominantly CSCs is now thought to be a primary course of treatment failure [36-40]. Many biological characteristics that enable cancer progression are attributable to CSCs, including angiogenesis, metastasis, and drug resistance. Early stage patients may benefit if the treatment does not fatally damage chemo-surveillance. The recovered chemo-surveillance capability may still be able to subdue CSCs which destruction therapy definitely cannot put away. There is no hope for the cure of advanced patients. The inability to put away CSCs and the contribution to destroy chemo-surveillance lay the ground for inevitable recurrence and fatality even the patients are fortunate to achieve complete remission. So cancer mortalities remain at old time high worldwide. Obviously, killing the majority of sensitive cancer cells cannot win the war on cancer. Some modifications must be done. Modifications to include agents effective on CSCs and to restore chemo-surveillance are very urgent to eliminate the deficiency of destructive agents to win the war on cancer [2,12,34-35,41-42].

War on cancer can be easily won if the battle is conducted following the nature's course to heal the wound, just like the success of wound healing without having to put up any effort in

healthy people. The key to the success of wound healing is the completion of TD of PSCs, which can be achieved with sufficient wound healing metabolites functioning as DIs and DHIs to destabilize abnormal MEs. Apparently, metabolites involved in wound healing are readily accepted into PSCs and CSCs protected by drug resistance mechanisms, which are most suitable agents for the termination of cells with drug resistance mechanisms. The success of cancer therapy depends greatly on the eradication of CSCs [35,42]. At present wound healing metabolites are the best hope to win the war on cancer [2,12,17].

5. CDA-2 AS A PERFECT CANCER DRUG

Perpetual cell replication is the hallmark of cancer. There are multiple issues involved to make cancer cells to replicate perpetually: the breakdown of cell membrane to become hyperpermeable because of destruction insults due to accidental injuries, surgery, infections, or toxic chemicals including carcinogens; the breakdown of chemo-surveillance due to membrane hyperpermeability sustained because of destruction insults to manifest cachexia symptom leading to the collapse of chemo-surveillance; the failure of wound healing due to the collapse of chemo-surveillance resulting in the evolution of PSCs to become CSCs; and the activation of oncogenes or inactivation of suppressor genes to progress to faster growing cancer cells. A perfect cancer drug must be the one that can resolve all issues involved in the evolution of cancer. CDA-2 is such a perfect cancer drug. CDA-2 was the invention of Liau [43], which was a preparation of natural wound healing metabolites purified from freshly collected male urine of college students by reverse phase chromatography employing XAD-16 as the adsorbent. It contains AA as a major DI, pregnenolone, steroid metabolites, and uroerythrin as DHIs, and phenylacetylglutamine as an active anti-cachexia chemical [12,43]. DIs and DHIs solve the blockade of differentiation to promote TD of cancer cells. By promoting TD, it also put to rest the issues of oncogenes and suppressor genes. Afterall oncogenes and suppressor genes are cell cycle regulatory genes. These genes have important roles to play when cells are in cell cycle replicating. But if replicating cells have exited cell cycle to undergo TD, they have no roles to play. Therefore, induction of TD is an easy solution of gene abnormalities which are otherwise very difficult to solve. Phenylacetylglutamine takes care of cachexia problem to prevent the loss of surveillance metabolites. So CDA-2 can take care of all important issues contributing to the development of cancer to qualify as a perfect cancer drug.

CDA-2 has been approved by the Chinese FDA for the therapy of MDS in 2017. MDS is a disease attributable entirely to CSCs [26]. In comparison to vidaza and decitabine, the two drugs approved by the FDA of USA, CDA-2 has a slightly better therapeutic efficacy based on cytological evaluation, and marked better therapeutic efficacy based on hematological improvement evaluation [2,44]. Cytological evaluation is based on the assessment of circulating cancer cells, and hematological improvement evaluation is based on the requirement of blood transfusion. Additionally, CDA-2 is devoid of serious adverse effects, whereas vidaza and decitabine are proven carcinogens [45], and very toxic to DNA [46-48]. Obviously, CDA-2 is the drug of choice for the therapy of MDS.

The therapeutic endpoint of CDA formulations is the TD of cancer cells. This endpoint is the same endpoint for the evaluation of hematological cancers undergoing destruction therapy. There is no problem for the acceptance of CDA-formulations for the therapy of hematological cancers. As for the therapy of MDS, these preparations should be considered as the standard of care, because the therapy of MDS requires the differentiation of pathological CSCs to become functional cells. The acceptance of CDA-formulations for the therapy of solid tumors is a problem, because the evaluation of the therapeutic endpoint is not available. Disappearance of tumor mass is not a valid therapeutic endpoint for CDA formulations. At present, they can be accepted for the therapy of untreatable cancers enriched with CSCs such as malignant brain tumors, pancreatic cancer, and melanoma. But for other more popular cancers, we can only hope to use CDA formulations as complementary therapy to assist whatever destruction therapy cannot accomplish such as the problems of CSCs, membrane hyperpermeability, cachexia, and chemo-surveillance. If surviving tumor mass is a fearful concern, combination therapy may be a solution. A combination with surgery is a perfect combination. Surgery to remove surviving tumor mass can eliminate fearful concern, and the application of CDA formulations can assure quick recovery of the surgical wound and the

prevention of possible metastasis. Treatment alternately with cytotoxic chemotherapy may be another winning combination for both, relying on cytotoxic drugs to eliminate tumor mass and CDA-formulations to eradicate CSCs and to restore chemo-surveillance. The combination with immunotherapy may be another winning combination. CSCs are PSCs minus TET-1 enzyme [3-4]. The immunity of CSCs is almost the same as that of PSCs, which is tolerable to the immune system. So even a successful immunotherapy is developed for cancer therapy, it may need CDA formulations to subdue CSCs. Therefore, CDA formulations are very helpful to assist other therapies to win the war on cancer.

6. CONCLUSION

Wound healing requires the proliferation and the TD of PSCs which are the precursors of CSCs. It takes only a single hit to silence TET-1 enzyme to convert PSCs to CSCs, which is well within the reach of PSCs equipped with abnormally active MEs. Therefore, the success of wound healing is very critical to avoid the evolution of cancer. Healthy people produce a steady level of chemo-surveillance metabolites active as DIs and DHIs, which are actually wound healing metabolites to ensure the success of wound healing. Wound healing metabolites acts on abnormal MEs to promote TD. When the functionality of chemo-surveillance is intact, wound healing can always be assured to avoid cancer. But if the functionality of chemo-surveillance is damaged due to chronic wound causing excessive urinary excretion of wound healing metabolites, then it is very likely that wound cannot be healed properly to let the proliferation of PSCs to continue beyond what is necessary to complete wound healing and to evolve into CSCs and then to progress to more faster growing cancer cells. The perfection of wound healing by the employment of wound healing metabolites active as DIs and DHIs and the prevention of the loss of wound healing metabolites with anti-cachexia chemicals such as phenylacetylglutamine is the best strategy to win the war on cancer. Destruction strategy to kill cancer cells definitely is inappropriate for cancer therapy. It creates more wounds to further damage the functionality of chemo-surveillance to the extent beyond restoration. Its inability to eradicate CSCs is a deciding factor to deny the success of destruction strategy to win the war on cancer.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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