On the Mechanism of Wound Healing and the Impact of Wound toward Cancer Evolution and Cancer Therapy: A Viewpoint

ABSTRACT

This viewpoint highlights the mechanism of wound healing and the impact of wound toward cancer evolution and cancer therapy. Wound healing requires the proliferation and the terminal differentiation (TD) of progenitor stem cells (PSCs). PSCs are pluripotent stem cells capable of undergoing differentiation to become various cells needed for the repair of the wound. Wound healing is deeply influenced by metabolites involved in chemo-surveillance and cachexia. Wound triggers production of prostaglandins (PGs) which play an essential role to promote the proliferation of PSCs at the initial stage of wound. At the final stage of wound healing, chemo-surveillance comes into play to induce TD of PSCs. The functionality of chemo-surveillance dictates the success of wound healing. The functionality of chemo-surveillance is usually intact in healthy people, so wounds typically heal naturally without adverse effect. Wound also triggers production of tumor necrosis factor (TNF) which is responsible for the display of cachexia symptom leading to the collapse of chemo-surveillance. TD of PSCs will be impaired, allowing PSCs to evolve into cancer stem cells (CSCs). It takes only a single hit to silence TET-1 enzyme to convert PSCs to become CSCs, which is well within the reach of PSCs because MEs of PSCs are abnormally active like cancer cells (CCs) due to association with telomerase. Wound healing and cancer evolution are closely related to involve PSCs as the critical common elements. Cancer can arise if wound is not healed properly. The most appropriate strategy for cancer therapy is to follow the successful process of wound healing. Cancer is caused by multiple factors that include the display of cachexia symptom, the breakdown of the functionality of chemo-surveillance, the blockade of differentiation, the evolution of CSCs, the activation of oncogenes, and the inactivation of suppressor genes. A perfect cancer drug must be able to solve all these important factors. Wound healing metabolites are the best candidates to fulfill such requirements.

INTRODUCTION

Wounds of healthy individuals typically heal without adverse effect. Since wound healing comes so easy, no body cares how wound is healed. However, if wound is not healed properly, serious consequence, such as the evolution of cancer may ensue. We should pay attention to how wound is healed so that the negative consequence of cancer can be avoided. The lesson of wound healing can also shed light on how to pursue appropriate therapy of cancer.

ON THE MECHANISM OF WOUND HEALING

Wound healing requires the proliferation and the TD of PSCs [1]. PSCs are the most primitive stem cells of adult body which are pluripotent stem cells capable of undergoing differentiation into various cells such as parenchyma and epithelial cells, connective tissues and blood vessels needed for the repair of the wound. These cells are protected by drug resistance mechanism to resist toxic chemicals, and express chemokine receptor to respond swiftly to signals for expansion or repair. Methylation enzymes (MEs) of these cells are abnormal like most cancer cells (CCs) due to association with telomerase [2]. The association of MEs with telomerase locks MEs in an exceptionally stable and active state to block TD [3, 4]. MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH) [5]. Destabilization of abnormal MEs by metabolites active as differentiation inducers (DIs) and differentiation helper inducers (DHIs) is an effective mechanism to induce TD of cells with abnormal MEs [3, 4]. DIs are chemicals capable of eliminating telomerase from abnormal MEs, and DHIs are inhibitors of ternary MEs which can greatly potentiate the activity of DIs. Destabilization of abnormal MEs through DIs and DHIs was the basic mechanism of chemo-surveillance we brought up as a natural defense against cancer [6]. The hypothesis of chemo-surveillance was based on the observation that healthy people were able to maintain a steady level of metabolites active as DIs and DHIs, whereas cancer patients tended to show deficiency of such metabolites due to excessive urinary excretion attributable to cachexia symptom. It turns out DIs and DHIs are wound healing metabolites. Thus, the primary objective of chemo-surveillance is to ensure perfection of wound healing to avoid cancer evolution.

Wound triggers biological and immunological responses. The biological response involves the release of arachidonic acid (AA) from membrane bound phosphatidyl inositol through phosphorlipase A2 for the synthesis of prostaglandins (PGs) by cyclooxygenases and PG synthases [7, 8]. Although AA and PGs are active DIs [9], the induction of TD of PSCs at the initial stage of wound is not the primary objective of PGs. Rather the localized inflammation caused by PGs [10] is responsible for the increase of membrane permeability in order to facilitate the extravasation of plasma proteins and regulatory factors into the wound resulting in edema response which is the primary objective of PGs to orchestrate the healing process. Chemo-surveillance mediated through DIs and DHIs is normally functioning as a brake to prevent the buildup of PSCs. This brake must be released in order for PSCs to produce enough

cells for the repair of wound. PGs are metabolically unstable [7]. Their biological effects are most likely brief and confined to the wound area. Thus, the promotion of the proliferation of PSCs is the primary objective of PGs on wound healing, whereas the induction of TD of PSCs at the final stage of wound healing is accomplished by wound healing metabolites involved in chemo-surveillance. The stable end products of PGs, namely bicycloPGs, may also participate in the final stage of wound healing. BicycloPGs are also active as DIs, although not as active as PGs [9]. The relatively inactive DIs of bicycloPGs can always be remedied by DHIs to boost their DI activity. Pregnenolone is a particularly good DHI to potentiate the DI activity of AA and related metabolites [9]. In short, the mechanism of wound healing requires the production of PGs to promote the proliferation of PSCs, and then the involvement of chemo-surveillance to induce TD of PSCs to complete wound healing process.

THE IMPACT OF WOUND TOWARD CANCER EVOLUTION

The immunological response of wound prompts the production inflammatory cytokines which are bad for wound healing. Tumor necrosis factor (TNF) among inflammatory cytokines (TNF) is particularly harmful. TNF is also named cachectin, a name after its responsibility to cause cachexia symptom. A characteristic disorder of cachexia is the excessive urinary excretion of low molecular weight metabolites because of leaky blood vessels caused by TNF [11, 12]. The loss of low molecular weight metabolites results in the collapse of chemo-surveillance and the incompletion of wound healing. Acute wound affects chemo-surveillance only temporarily, which is quickly restored to the normal state. The good effect of biological response to wound usually prevails in this case. It is the chronic wound that produces a persistent damage to the functionality of chemo-surveillance to impair the ability to heal wound, resulting in cancer evolution. If wound is not healed properly, the continuous proliferation of PSCs runs a risk to evolve into CSCs. A single hit to silence TET-1 enzyme can convert PSCs to become CSCs [13], which is a task well within the reach of PSCs equipped with abnormally active MEs. Therefore, the functionality of chemo-surveillance is so important to ensure the perfection of wound healing to avoid cancer evolution [14].

Myelodysplastic syndrome (MDS) is a classic example of cancer evolution due to wound not healing properly. MDS often starts with a display of immunological disorder [15]. Which prompts the production of inflammatory cytokines. Among cytokines produced, TNF is the critical factor related to the development of MDS [16]. It causes excessive apoptosis of bone marrow stem cells, thus severely affects the ability of the patient to produce hematopoietic cells such as erythrocytes, platelets, and neutrophils. TNF is responsible for the display of cachexia symptom which is commonly shared by cancer and inflammatory patients. Cachexia symptom causes the collapse of chemo-surveillance as above described. 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 is an indication of the widespread multiplication of PSCs [17, 18]. During the course of MDS progression, mutations affecting enzymes were frequently observed [19-21], which might play significant roles in the evolution of PSCs to become CSCs [22]. 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 acute myeloid leukemia (AML) [23-26].

Evolution of cancer due to wound not healing properly is not unique to AML. It is rather a common occurrence. We have previously observed that the protection of the integrity of chemo-surveillance by Antineoplaston A10, namely phenylacetylglutamine, could effectively prevent chemical carcinogenesis [27, 28], and achieve an effective therapy of early stage cancer [6]. We have also noticed that abnormal MEs were detectable in preneoplastic hyperplastic nodules before the appearance of carcinomas during chemical hepatocarinogenesis [29]. Obviously, carcinomas were derived from cells expressing abnormal MEs in the preneoplastic state, which were very likely PSCs. The occurrence of human cancer and experimental animal cancer all points to PSCs as the origin of cancer, and imperfection of wound healing is the culprit.

THE IMPACT OF WOUND TOWARD CANCER THERAPY

We were not alone to notice that cancer arose as a consequence of wound not healing properly [1]. MacCarthy-Morrough and Martin made a similar observation to propose that the hallmarks of cancer were also the hallmarks of wound healing [30]. Since cancer arises due to wound not healing properly, perfection of wound healing is the most appropriate strategy for cancer therapy [1, 31, 32]. It is clear that cachexia symptom is responsible for the collapse of chemo-surveillance, and the collapse of chemo-surveillance allows PSCs to evolve into CSCs which are then progressed to faster growing CCs. The elimination of cachexia symptom and the restoration of the functionality of chemo-surveillance become an important matter for the success of cancer therapy [33]. In this regard, phenylacetylglutamine may have an important role to play, which we have found effective to prevent excessive urinary excretion of low molecular weight metabolites to restore the functionality of chemo-surveillance [6, 27, 28].

CSCs are originated from PSCs. Naturally, CSCs display cell features and biological missions very similar to PSCs. Both PSCs and CSCs express ATP binding drug pumps that can effectively exclude toxic chemicals and have upregulated anti-apoptosis programs that negate the pro-apoptotic signals activated by DNA damaging therapies [34-37]. Thus, these cells are resistant to cytotoxic drugs and radiation. These cells normally reside in acidic and hypoxic microenvironments hard to reach by the blood stream. They remain dormant unless situations such as wound arise that stimulate their recruitment. Although CSCs constitute only a small side population, they are the primary causes of treatment failure in the past based on destruction strategy [38-40]. Primary causes of treatment failure such as metastasis, drug resistance, angiogenesis, and recurrence can all attribute to CSCs. It is apparent that CSCs stand in the way to deny the success of destruction therapies to put cancer away in the past [1, 31, 41]. Therefore, the ability of the drug to eradicate CSCs becomes an important consideration for the evaluation as cancer drugs [42]. Since CSCs reside in microenvironments hard to reach by the blood stream, small molecules easily diffusible, such as, wound healing metabolites are a better choice. In fact, such molecules are routinely employed by PSCs on wound healing. Wound

healing metabolites are, after all, the partners of the biological missions of PSCs and CSCs, they are easily tolerated by these cells protected by drug resistance mechanism. CDA-2 was a preparation of wound healing metabolites purified from freshly collected human urine [43]. CDA-2 is obviously a drug of choice for the therapy of MDS since it has better therapeutic efficacies than vidaza and decitabine, the two US approved drugs, both on cytological evaluation and hematological improvement evaluation [44, 45]. Better yet, CDA-2 is totally devoid of serious adverse effects, whereas vidaza and decitabine are proven carcinogens and very toxic to DNA [46-49]. MDS is a disease attributable entirely to CSCs [22]. Thus, wound healing metabolites are proven drugs to display clinical efficacy against CSCs.

Destabilization of abnormal MEs by means of DJs and DHIs is the critical mechanism of wound healing. It is also the most appropriate strategy for cancer therapy. One may argue that abnormal MEs cannot be considered a specific cancer target since abnormal MEs are also detectable in primitive stem cells such as embryonic stem cells and PSCs. But the silencing of TET-1 enzymes in CSCs and CCs qualifies abnormal MEs as a specific cancer target. Targeted therapies are always better therapies that can avoid adverse effects. Unfortunately, in cancer therapy, destructive agents are privileged because cancer establishments set up disappearance of tumor as the most important criterion for the evaluation of therapeutic efficacy. Targeted therapies which do not cause cell death are excluded from consideration as cancer drugs. Destructive agents such as cytotoxic drugs and radiation are apparently contraindication on cancer therapy. They create more wound to aggravate the already bad situation. Their inability to eradicate CSCs and their contribution to further damage chemo-surveillance lay the ground for inevitable recurrence and fatality. So even the fortunate few who have achieved complete remission through destructive therapies are eventually succumbed to recurrence. That is why cancer mortalities remain at old time high worldwide. Perhaps a very few early stage cancer patients whose functionality of chemo-surveillance is not fatally damaged in the process can restore the functionality of chemo-surveillance to subdue surviving CSCs. Disappearance of tumor definitely is a questionable therapeutic endpoint for the evaluation of cancer therapy. Other criteria must be considered such as the disappearance of circulating CCs and CSCs, the disappearance of cancer markers, and the restoration of the functionality of chemo-surveillance Gene therapy is of course the most fascinating and attractive field. Correction of abnormal genes is a very difficult task. Even if a gene abnormality is successfully corrected, another gene abnormality may possibly arise. It becomes an endless struggle to correct difficult gene abnormalities. Oncogenes and suppressor genes are, after all, cell cycle regulatory genes. They have important roles to play when cells are in cell cycle replicating. But if cells exit the cell cycle to undergo TD, they have no roles to play. So a stroke to destabilize abnormal MEs can also put to rest abnormal gene problems. Abnormal MEs can be considered as the bullseye of targeted cancer therapies[50].

CONCLUSION

Wound healing and the evolution of cancer are closely related to involve PSCs as the critical common elements. The study of the mechanisms of wound healing and the impact of wound toward cancer evolution and cancer therapy can shed light on more appropriate strategies for

cancer therapy. The mechanisms of wound healing is mediated by PGs to promote the proliferation of PSCs and by DIs and DHIs to induce TD of PSCs. Cancer arises as a consequence of wound not healing properly, allowing PSCs to evolve into CSCs, and then to progress to faster growing CCs. Destabilization of abnormal MEs, which is the critical mechanism of successful wound healing, is the most appropriate strategy for cancer therapy. A big problem remains as this strategy cannot make tumor to disappear.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. 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.

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