

On the Mechanism of Wound Healing and the Impact of Wound on Cancer Evolution and Cancer Therapy

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ABSTRACT

This opinion article highlights the mechanism of wound healing and the impact of wound on 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 the production of prostaglandins (PGs) which play an essential role to promote the proliferation of PSCs at the initial stage of the 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 nicely without having to put up any efforts. Wound also triggers production of tumor necrosis factor (TNF) which is responsible for the display of cachexia symptoms 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 evolution of cancer are so closely related to involve PSCs as the critical common elements. Cancer can arise if a wound is not healed properly. The most appropriate strategy for cancer therapy is to follow successful process of wound healing. The appropriate strategy must be able to eliminate cachexia symptoms, to restore the functionality of chemo-surveillance, to eradicate CSCs, to eliminate differentiation blockade, and to put away oncogenes and cancer suppressor genes. Wound healing metabolites are the best candidates to fulfill such requirements.

INTRODUCTION

Wounds in healthy people are usually healed without having to put up any effort. Wound healing is a natural human response, nobody cares how a wound is healed. However, if wound is not healed properly, serious consequences, such as the evolution of cancer may ensue. We have better to pay attention on how the wound is healed so that bad consequence of cancer can be avoided. The lesson of wound healing can also shed light on how to pursue appropriate therapy of cancer.

OPINIONS AND DISCUSSIONS

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 the adult body which are pluripotent stem cells capable of 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 a drug resistance mechanism to exclude toxic chemicals, and express chemokine receptors 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) are 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 symptoms. 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 phosphatidylinositol through phospholipase 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 the wound is not the primary objective of PGs. Rather the localized inflammation caused by PGs [10] is responsible for the increase of membrane permeability 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 normally functions 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 the 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 may also participate in the final stage of wound healing. The stable end products of PGs are also active as DIs, although not as active as PGs [9]. The relatively inactive DIs of the endproducts of PGs can always be remedied by DHIs to boost their 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 ON CANCER EVOLUTION

The immunological response prompts the production inflammatory cytokines which are bad for wound healing, particularly tumor necrosis factor (TNF) which is also named cachectin, a name to characterize its effect on cachexia symptoms. 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 incompleteness of wound healing. Acute wound affects chemo-surveillance only temporarily, which is quickly recovered 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 cancer stem cells (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 an immunological disorder [15]. This disorder 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 affecting the ability of the patient to produce hematopoietic cells such as erythrocytes, platelets, and neutrophils. TNF is responsible for the cachexia symptoms which is commonly shared by cancer and inflammatory patients. Cachexia symptoms 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 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].

The 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 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 hepatocarcinogenesis [29]. Carcinomas were derived from cells expressing abnormal MEs in the preneoplastic state, which were very likely PSCs. So the occurrence of human cancer and experimental animal cancer all point to PSCs as the origin of cancer, and imperfection of wound healing is the culprit.

THE IMPACT OF WOUND ON CANCER THERAPY

We were not alone to notice that cancer arose as a consequence of wound not healing properly [1]. MacCarthy-Morrugh and Martin made a similar observation that the hallmarks of cancer are also the hallmarks of wound healing [30]. 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 allow PSCs to evolve into CSCs which can progress to faster growing CCs. Elimination of cachexia symptoms and 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 bloodstream. They remain dormant unless situations such as wounds arise that stimulate their recruitment. Although CSCs constitute only a small side population, they are the primary cause 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 of cancer drugs [42]. Since CSCs reside in microenvironments hard to reach by the bloodstream, 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. After all, wound healing metabolites are the partners of the biological missions of PSCs and CSCs, they

are easily tolerated by these cells equipped with 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 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 DIs and DHIs is the critical mechanism of wound healing. It is also the most appropriate strategy for cancer therapy. Abnormal MEs are also detectable in primitive stem cells such as embryonic stem cells and PSCs, so that they cannot be considered a specific cancer target. But the silencing of TET-1 enzyme in CSCs and CCs qualifies abnormal MEs as a specific cancer target. Targeted therapies are always better therapies to 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 for 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. May be a very few early stage cancer patients whose functionality of chemo-surveillance is not fatally damaged in the process can recover to subdue surviving CSCs. Disappearance of tumor definitely is a questionable therapeutic endpoint for the evaluation of cancer therapy. Other criteria must be established such as disappearance of circulating CCs and CSCs, disappearance of cancer markers, restoration of the functionality of chemo-surveillance, etc. Gene therapy is of course the most fascinating and attractive field. To correct abnormal gene is a very difficult task. Even one gene abnormality is successfully corrected, there may soon pop up another gene abnormality. It is 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 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 mechanism of wound healing and the impact of wound on cancer evolution and cancer therapy can shed light on more appropriate strategy for cancer therapy. The mechanism of wound healing is mediated by PGs to promote the proliferation of PSCs and by DIs and DHIs to direct TD of PSCs. Cancer arises as a consequence of the wound not

healing properly, allowing PSCs to evolve into CSCs, and then to progress to faster growing CCs. Destabilization of abnormal MEs, exactly the same strategy of successful wound healing, is the most appropriate strategy for cancer therapy. There remains a big problem. This strategy cannot make tumors to disappear.

COMPETING INTERESTS DISCLAIMERS

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly used products of our area of research and country. There is no conflict of interest between the authors and the 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 producing company rather it was funded by personal efforts of the authors.

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