No Scar as an Indication of Perfect Wound Healing, Ugly Scar as Imperfect Wound Healing, and Cancer as Failed Wound Healing

ABSTRACT

Wound healing and cancer evolution are closely related to involve progenitor stem cells (PSCs) as the critical common elements. Wound healing requires the proliferation and the terminal differentiation (TD) of PSCs. Wound triggers biological and immunological responses. The biological response prompts the release of arachidonic acid (AA) from membrane bound phosphatidylinositol for the synthesis of prostaglandins (PGs) which are active differentiation inducers (DIs) good for wound healing. Immunological response prompts the production of tumor necrosis factor (TNF) to cause cachexia symptom leading to the breakdown of chemo-surveillance bad for wound healing. The proliferation of PSCs is promoted by PGs and the TD of PSCs is accomplished by metabolites involved in chemo-surveillance. Thus, the functionality of chemo-surveillance plays an important role to dictate the success of wound healing. If the functionality is perfect as healthy people, healing of wound with no scar can always be expected. But if the functionality of chemo-surveillance has been damaged due to pathological conditions causing cachexia symptom, then healing of wound may be impaired to result in ugly scar. Ugly scar in visible surface is a medical concern, particularly with respect to cosmetic surgery. CDA-WH, an ointment preparation for wound healing, is recommended to ensure perfect wound healing with no scar. Cancer arises as a consequence of failed wound healing due to extensive breakdown of chemo-surveillance to allow replicating PSCs to evolve into cancer stem cells (CSCs). A single hit to silence TET-1 enzyme is enough to convert PSCs to become CSCs, which is a task that can be easily accomplished by PSCs equipped with abnormally active methylation enzymes (MEs). Subsequent activation of oncogenes, and/or inactivation of suppressor genes turns CSCs to progress to faster growing cancer cells (CCs). These are exactly the sequences taking place in the generation of acute myeloid leukemia (AML) from bone marrow PSCs to myelodysplastic syndrome (MDS) and then to AML. Cancer therapy following the course of successful wound healing is the most appropriate modality of cancer therapy, whereas cytotoxic agents are contraindication. Cancer therapy through wound healing metabolites can restore the functionality of chemo-surveillance, eliminate the blockade of differentiation, eradicate CSCs, and put to rest problems arising from gene abnormalities, which is a model of perfect cancer therapy. Cytotoxic agents are good to eliminate CCs, but they create more wounds 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 few fortunate patients to achieve complete response are eventually succumbed to recurrence.

Key Words: wound healing, chemo-surveillance, no scar, ugly scar, cancer.

INTRODUCTION

Wound healing has never been regarded as an important medical issue, because wounds are always healed naturally without having to put up any effort. But if wounds are not healed properly, bad consequences may ensue. Cancer is the most feared bad consequence of wounds not healing properly [1-3]. Since cancer is such a dreadful disease, we must pay attention to the issue of wound healing. This article brings up deep discussions of wound healing for the purpose of seeking no scar healing to accomplish perfect surgery. No scar healing is an absolute requirement for cosmetic surgery. The study of perfect wound healing process may shed light on more appropriate modality of cancer prevention and therapy.

OPINIONS AND DISCUSSIONS

On the Mechanism of Wound Healing

Wound triggers biological and immunological responses. The biological response involves the release of AA from membrane bound phosphatidylinositol by phospholipase A2 for the synthesis of PGs by cyclooxygenases and PG synthases [5, 6]. PGE2 is essential for the efficacious wound healing, because the inhibition of PGE2 synthesis results in the impairment of wound healing [5]. Although PGs were found active as differentiation inducers (DIs) [7, 8], we have reasoned that the localized inflammatory effect of PGs [9] to release DIs and differentiation helper inducers (DHIs), which functioned as a brake to inhibit the proliferation of PSCs, from inside of PSCs was the real function of PGs in wound healing [3]. Wound healing requires the proliferation of PSCs which are the most primitive stem cells of the adult body. PSCs are pluripotent stem cells capable of undergoing differentiation to become various cells such as parenchyma and epithelial cells, connective tissues and blood vessels needed for the repair of the wound. The buildup of PSCs is an important aspect of wound healing. But the induction of TD of PSCs is also an important aspect of wound healing, which is accomplished by the components involved in chemo-surveillance. Therefore, the functionality of chemo-surveillance plays an important role to dictate the success of wound healing [10].

Chemo-surveillance Revisited

Chemo-surveillance was a hypothesis brought up by Liau et al. [11] as a natural defense mechanism against cancer. This hypothesis 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 deficiencies of such metabolites due to display of cachexia symptom. A characteristic disorder of cachexia is the excessive urinary excretion of low molecular weight metabolites including DIs and DHIs involved in chemo-surveillance. DIs and DHIs are metabolites capable of modulating differentiation of cells with abnormal MEs. MEs of cancer cells (CCs) are abnormal due to association with telomerase [12]. The association of MEs with telomerase locks MEs in an exceptionally stable and active state to block TD of CCs [13, 14]. DIs are chemicals capable of eliminating telomerase from abnormal MEs, and DHIs are inhibitors of the ternary MEs consisting of methionine adenosyltransferase-methyltransferase-

S-adenosylhomocysteine hydrolase [15]. MEs of PSCs are abnormal like CCs. Wound healing metabolites responsible for the induction of TD of PSCs are the metabolites involved in the execution of chemo-surveillance. Thus, the primary objective of chemo-surveillance is to ensure perfection of wound healing. The defense against cancer is the secondary consequence.

Metabolites active as DIs and DHIs are hydrophobic metabolites that can be purified from urine by reverse phase chromatography. C18 and XAD-16 are frequently used as adsorbants in reverse phase chromatography. Wound healing metabolites purified by C18 were named Antineoplastons by Burzynski [13, 14, 16, 17], and those purified by XAD-16 were named cell differentiation agent-2 (CDA-2) by Liau [18, 19]. Peptides are important urinary DIs of Antineoplastons, but are not recovered in CDA-2. We used peptides as the surrogate molecules for the study of chemo-surveillance [11]. Since the urinary peptide profile was similar to the peptide profile of spleen extract, we have suggested that the breakdown products of erythrocytes were a major source of urinary DIs [20]. Spleen is known as an organ to process dead erythrocytes. The finding of uroerythrin as the most active DHI of Antineoplastons and CDA-2 supported our belief [21]. We still do not know the identity of urinary peptides active as DIs. Organic acids designated as OA-0.79 and membrane fragments designated as PP-0 were other urinary DIs of Antineoplastons [16, 17], which are also the major DIs of CDA-2 [18, 19]. We have identified AA-pregnenolone mixture as OA-0.79, and AA as the active DI of PP-0 [19, 22]. It appears that AA in liposomal complexes with pregnenolone and bound to membrane fragments are the major DIs of wound healing metabolites. Steroid metabolites constitute important urinary DHIs [23], which must be produced by other sources such as adrenal gland and liver.

Wound healing and evolution of cancer are closely related to involve PSCs as the critical common elements. Wound healing requires the proliferation of PSCs, which always runs a risk for PSCs to evolve into CSCs. The evolution of CSCs from PSCs is very simple. A single hit to silence TET-1 enzyme can convert PSCs to become CSCs, which is a task easily accomplished by PSCs equipped with abnormally active MEs [24]. Chemo-surveillance is a very important mechanism to prevent that from happening. Protection of the functionality of chemo-surveillance is, therefore, very important to ensure perfection of wound healing to avoid cancer evolution. Pathological conditions prompt the production of TNF must be carefully watched and treated. Wound, inflammatory diseases and cancer all trigger immunological responses to produce inflammatory cytokines. TNF among such cytokines is critically related to the display of cachexia symptom. TNF is also named cachectin to refer to its biological effect to cause cachexia symptom. A characteristic disorder of cachexia is the excessive urinary excretion of low molecular weight metabolites because of vascular hyperpermeability caused by TNF [25, 26]. As a consequence, chemo-surveillance operating in healthy people to keep PSCs in check becomes dysfunction to affect the process of wound healing.

Since the functionality of chemo-surveillance plays an important role to dictate the success of wound healing and cancer therapy, the evaluation of the functionality is valuable for the consideration of surgery and cancer therapy. The functionality of chemo-surveillance can be evaluated by quantitative assay of important wound healing metabolites such as peptides [11],

AA [22], pregnenolone [19], or uroerythrin [21]. Quantitative assay of pregnenolone can be done by commercial diagnostic service. Take the quantitative assay of peptides we have done before [11] as an example, we can assign plasma/urine peptide ratios of 0.8 as CDA 4+ (CDA 4+,TNF 0), 0.6 as CDA 3+ (CDA 4+, TNF 1+), 0.4 as CDA2+ (CDA 4+, TNF 2+), 0.2 as CDA 1+ (CDA 4+, TNF 3+), and less than 0.1 as CDA 0 (CDA 4+,TNF 4+). Persons with the score as CDA 4+ and TNF 0 do not have to worry about wound healing. Persons with the score of low CDA and high TNF have a lot to worry on wound healing and cancer therapy.

Phenylacetylglutamine is a very good anti-cachexia agent to boost CDA scores and to reduce TNF scores Treatment with phenylacetylglutamine may be helpful for the success of wound healing and cancer therapy [11]. In fact, phenylacetylglutamine has been successfully employed to prevent chemical carcinogenesis [27, 28] and therapy of early stage cancer [11].

No Scar as an Indication of Perfect Wound Healing

The functionality of chemo-surveillance in healthy people is usually perfect, and inflammatory conditions none. We can assign healthy people a score of CDA 4+ and TNF 0. Acute wound from surgery and accidental injuries may yield more PGs than TNF to boost a score of net 1+ on CDA to healthy persons to CDA 5+ that can efficiently heal the wound with no scar. No wonder wound healing is not a concern for healthy people. PSCs are after all normal stem cells. Normal stem cells always obey the rule of contact inhibition. There is no worry of PSCs to pile up to result in ugly scar. Even with the presence of limited CSCs, which do not obey the rule of contact inhibition, efficient TD of PSCs and CSCs with high score of CDA 5+ can result in no scar.

Ugly Scar as Imperfect Wound Healing

Surgery is usually performed on patients with illnesses. Such patients have CDA less than 4+ and TNF more then 0. Wounds resulting from burn and pathological conditions such as toxic agents, infectious diseases, and senescent cells yield more TNF than PGs to result in net loss of CDA to CDA 3+ or less.. The efficient wound healing on persons with CDA scores of less than 3+ cannot be expected. Without enough CDA components, CSCs may pile up to result in ugly scar if CSCs are eventually induced to undergo TD. Nobody cares ugly scar that happened internally. But everybody cares external scar, particularly on the exposed surface. Treatments with CDA formulations must be considered to deal with the ill effects of imperfect wound healing. It is a good policy to employ CDA-WH, WH stands for wound healing, ointment to assure no scar wound healing. To make effective CDA formulations, the formulations can be $3xED_{25}$ of DI + $1xRI_{0.5}$ of DHI; or $2xED_{25}$ of DI + $2xRI_{0.5}$ of DHI; or $1xED_{25}$ of DI + $3xRI_{0.5}$ of DHI. We have published many effective DIs and DHIs to choose from [7, 8, 23, 29].

Cancer as Failed Wound Healing

The worst case of wound not healing properly is the evolution of cancer if the functionality of chemo-surveillance has been damaged to the extent unable to effectively put away CSCs. The progress of CSCs to faster growing CCs is just a matter of time. These are exactly the

sequence of events taking place on the evolution of CSCs from bone marrow PSCs to become myelodysplastic syndrome (MDS), and then progress to become acute myeloid leukemia [1, 24]. The best solution of cancer is to follow the course of successful wound healing. That is to eliminate TNF, which is responsible for cachexia symptom, to protect the functionality of chemo-surveillance. The functionality of chemo-surveillance can ensure the perfection of wound healing to avoid cancer. CSCs are originated from PSCs. PSCs and CSCs are almost alike on cell features and biological missions. They are protected by drug resistance mechanism to exclude toxic agents. Wound healing metabolites are the partners to their biological missions. Therefore, wound healing metabolites are easily tolerated by PSCs and CSCs. Wound healing metabolites are the best hope to take out PSCs and CSCs. Cytotoxic agents are very good to kill CCs. But they are contraindication on cancer therapy. They create more wounds to aggravate the already bad situation. Their inability to take out CSCs and their contribution to further damage chemo-surveillance lay the ground for inevitable recurrence and fatality. That is why cytotoxic agents dominate cancer therapy in the past for a very long time, but cancer mortalities remain at all time high [30]. The best solution of cancer is to follow the successful course of wound healing process by employing CDA-CSC to induce TD of PSCs, CSCs, and CCs. The super ugly scar can be safely removed by surgery when cancer patients have recovered to the status of CDA 3+ and TNF 1+.

CONCLUSION

Wound healing and cancer evolution are closely related to involve PSCs as the critical common elements. Wound healing requires the proliferation and the TD of PSCs. The proliferation of PSCs requires PGs and the TD of PSCs requires CDA, the wound healing metabolites. The functionality of chemo-surveillance, thus, play an important role to dictate the success of wound healing. As shown in Figure 1, the functionality of chemo-surveillance, designated as CDA 0 to 4+, dictate the success of wound healing to yield no scar, ugly scar, and cancer. Obviously ugly scar and cancer are the consequences of wound not healing properly, therapies employing CDA formulations are the best remedies to ensure no scar wound healing and cancer therapy.

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.

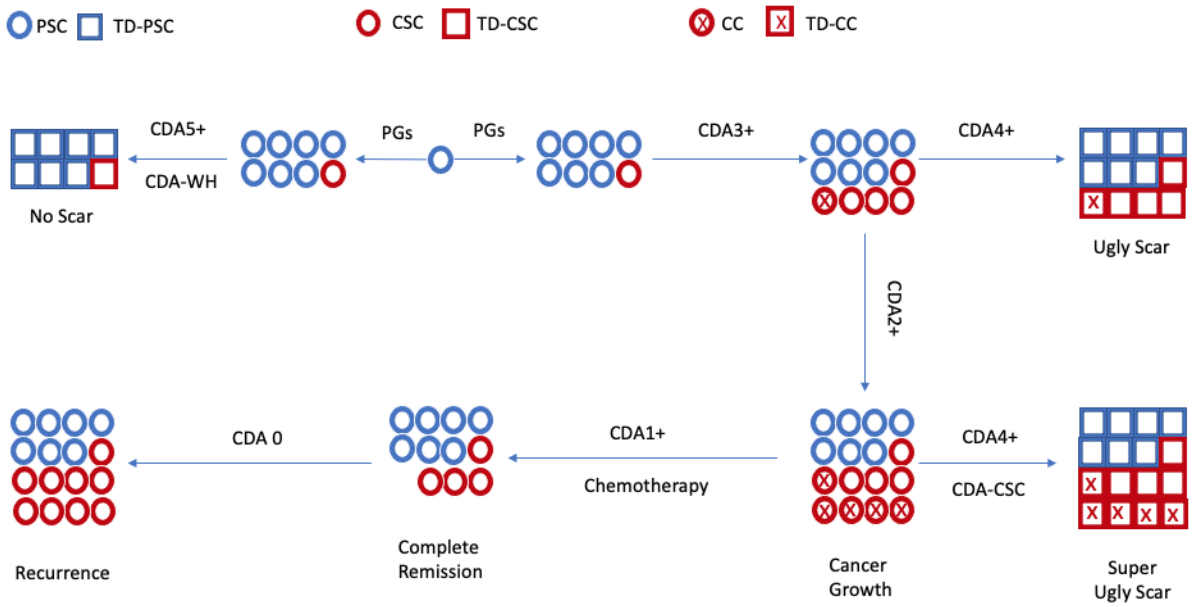

Figure 1. Role of chemo-surveillance to dictate wound healing

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