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Opinion

The Proliferation and the Terminal Differentiation of Progenitor Stem Cells Determine the Success of Wound Healing. Likewise, the Proliferation and the Terminal Differentiation of Cancer Stem Cells Determine the Success of Cancer Therapy

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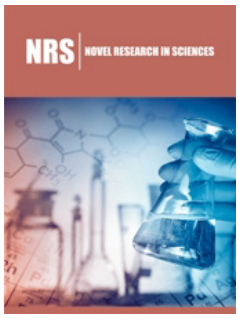

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Submission: March 08, 2021

Published: March 09, 2021

Volume 6 - Issue 3

How to cite this article: Liau MC, Baker LL. The Proliferation and the Terminal Differentiation of Progenitor Stem Cells Determine the Success of Wound Healing. Likewise, the Proliferation and the Terminal Differentiation of Cancer Stem Cells Determine the Success of Cancer Therapy. Nov Res Sci. 6(3). NRS. 000636.2021.
DOI: 10.31031/NRS.2021.06.000636

On Wound Healing, We Let the Nature to Take Its Course to Heal the Wound

Wound healing and the evolution of cancer are closely related to involve progenitor stem cells (PSCs) as the critical common elements. PSCs and cancer stem cells (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 [1,2]. PSCs are still able to carry out differentiation programs, relying on TET-1 enzyme to achieve DNA hypomethylation required for the cell to undergo terminal differentiation (TD) [3]. The differentiation capability of CSCs is completely blocked. PSCs are the most primitive stem cells which 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 the damages. PSCs express ATP binding cassette drug pumps that can effectively exclude toxic chemicals [4] and have anti-apoptosis programs that can negate apoptosis signals activated by DNA damaging radiation [5]. PSCs normally reside dormantly in acidic and hypoxic microenvironment hard to reach by the blood. PSCs express chemotactic receptors, thus sensitive to signals calling for the expansion or repair. Methylation enzymes (MEs) of PSCs are abnormal like cancer cells due to the association with telomerase [6], making differentiation hard to proceed. Hindrance of differentiation may be a critical mechanism to buildup cell mass for PSCs to repair the wound. The proliferation and the TD of PSCs are 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) [7], which are active differentiation inducers (DIs) good for wound healing to terminate the proliferation of PSCs [8]. 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 progress to faster growing cancer cells. The immunological response prompts the production of inflammatory cytokines which are bad for wound healing. Among inflammatory cytokines, tumor necrosis factor (TNF) is the most damaging [9]. 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 [10]. The metabolites responsible for chemo-surveillance are the metabolites involved in wound healing [8]. Therefore, the perfection of wound healing

is the natural defense mechanism to avoid cancer. When chemo-surveillance is intact such as healthy people, perfect wound healing can always be anticipated. If chemo-surveillance is compromised such as persons suffering chronic immunological disorders or exposure to toxic chemicals for a long time, then the wound cannot be healed properly to eventually becoming cancer patients [11].

Metabolites involved in wound healing are readily accepted into PSCs protected by drug resistance mechanism, and abnormal MEs are the target of wound healing metabolites to direct TD of PSCs to successfully healing the wound. Destabilization of abnormal MEs is the key to the success of wound healing. PGs are obviously the most active DIs to achieve induction of TD of PSCs. DIs are chemicals capable of eliminating telomerase from abnormal MEs. Induction of TD by DI requires the participation of differentiation helper inducers (DHIs), which are the inhibitors of the ternary MEs, to reach completion. DI alone always causes damages to some cells in the sensitive stage during the process of TD to interrupt the differentiation process. The damaged cells can later repair the damages to revert back to the uninduced state. The presence of DHIs can prevent damages to perfect TD of PSCs or CSCs. This is the reason that the capability of chemo-surveillance is essential to the success of wound healing, because it provides the needed DHIs to perfect wound healing and to avoid cancer. From wound healing we learn that metabolites involved in wound healing are very valuable for us to develop drugs to target CSCs. The eradication of CSCs is the key to the success of cancer therapy [12].

CDA-2 as a Perfect Cancer Drug

Cancer is a disease caused by multiple issues: membrane hyperpermeability, cachexia, blockade of differentiation, activation of oncogenes, and inactivation of suppressor genes all contribute significantly to display clinical symptom of perpetual cell proliferation. A perfect cancer drug must be the one that can resolve all issues contributing to the development of cancer. Cell differentiation agent-2 (CDA-2) is such a perfect cancer drug. CDA-2 was the invention of Liau [13], which was a preparation of natural metabolites involved in wound healing 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 [14]. DIs and DHIs solve the blockade of differentiation to promote TD. By solving the blockade of differentiation, 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 exit 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 restore chemo-surveillance capability. So CDA-2 can take care of all important issues contributing to the development of cancer to qualify it as a perfect cancer drug.

CDA-2 has been approved by the Chinese FDA for the therapy of myelodysplastic syndrome (MDS) in 2017. MDS is a disease attributable entirely to CSCs [15]. MDS can be used to test the drugs effective against CSCs. Metabolites effective for wound healing are very likely to pass the test like CDA-2. 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 [16,17]. Additionally, CDA-2 is devoid of serious adverse effects, whereas vidaza and decitabine are proven carcinogen [18], and very toxic to DNA [19-21]. Obviously CDA-2 is the drug of choice for the therapy of MDS.

Destabilization of abnormal MEs is the critical mechanism of CDA-formulations to achieve TD of cancer cells. TD is the endpoint for the evaluation of therapeutic efficacy of CDA-formulations. This endpoint is the same endpoint for the evaluation of hematological cancers undergoing destruction therapies. There is no problem for the acceptance of CDA-formulations for the therapy of hematological cancers. As for 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 agents to assist whatever cannot be accomplished by destruction therapies such as the problem of CSCs, the cachexia problem, and the destruction on chemo-surveillance.

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