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Opinion

The Functionality of Chemo-surveillance Dictates the Success of Wound Healing as Well as Cancer Therapy

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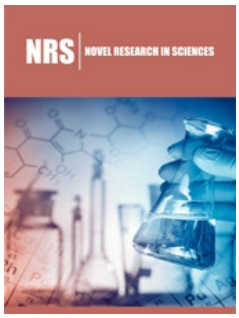

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The Functionality of Chemo-Surveillance

Chemo-surveillance was a natural defense mechanism against cancer brought up by Liau et al. [1] to describe the ability of healthy people to produce metabolites to prevent the evolution of cancer. It turns out that the functionality of chemo-surveillance is really an important mechanism to dictate the success of wound healing as well as cancer therapy, because metabolites involved in chemo-surveillance are the metabolites involved in wound healing [2]. Wound healing and the evolution of cancer are closely related to involve Progenitor Stem Cells (PSCs) as the critical common elements [3,4]. Therefore, the primary objective of chemo-surveillance is to ensure the success of wound healing. Human body produces metabolites active as Differentiation Inducers (DIs) and Differentiation Helper Inducers (DHIs) to keep a check on the proliferation of cells with abnormal Methylation Enzymes (MEs). MEs of cancer cells and PSCs are abnormal due to association with telomerase [5]. Abnormal MEs play important roles to block cell differentiation and to promote malignant growth. The proliferation and the Terminal Differentiation (TD) of PSCs are the most critical events in wound healing. DIs and DHIs, which can regulate the activity of abnormal MEs, play important roles on wound healing and cancer therapy. DIs are chemical capable of eliminating telomerase from abnormal MEs, and DHIs are inhibitors of ternary MEs. DIs are more important than DHIs on the induction of TD. DHIs are totally ineffective without DIs [6]. 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 [2,6]. The damages are very likely caused by the conversion of methyltransferases to become nucleases when ternary MEs are dissociated into monomeric enzymes. Such damages can be prevented in the presence of DHIs to achieve completion of TD. DIs and DHIs of plasma and urine are primarily the degradative products of erythrocytes and steroid metabolites. We have found peptides, arachidonic acid in liposomal complexes with pregnenolone designated as OA-0.5 and in association with membrane fragments designated as PP-0 as the major DIs, and uroerythrin, and steroid metabolites as the most active DHIs [7-10].

Wound incites biological response and immunological response. Biological response involves the breakdown of membrane bound phospholipid to release Arachidonic Acid (AA) for the synthesis of Prostaglandins (PGs), which are good for wound healing [2,3]. The immunological response prompts the production of inflammatory cytokines, which are bad for wound healing [11,12]. When the functionality of chemo-surveillance is intact, the good effect of biological response prevails to result in perfect wound healing. The breakdown of membrane bound phospholipid facilitates membrane hyperpermeability to release DIs and DHIs, which function as a brake to inhibit the proliferation of PSCs, out of PSCs to promote the proliferation of PSCs. The production of PGs, which are very active DIs [2], and sufficient wound healing metabolites can assure perfect TD of PSCs to heal the wound.

This is the natural way of wound healing which has never failed when the functionality of chemo-surveillance is intact. But when the functionality of chemo-surveillance breaks down such as the case of immunological disorder [11], then the bad effect of inflammatory

cytokines prevails to result in the continuous proliferation of PSCs beyond what is necessary for wound healing. The unchecked proliferation of PSCs can easily evolve to become Cancer Stem Cells (CSCs) by a single hit to silence TET-1 enzyme [13,14], a biological process well within the reach of PSCs equipped with abnormally active MEs. CSCs can then progress to faster growing cancer cells by activation of oncogenes or inactivation of suppressor genes. It is very common that cancer can evolve as a consequence of wound not healing properly due to the collapse of the functionality of chemo-surveillance. Chronic immunological disorder can cause the collapse of chemo-surveillance. Chronic toxic chemical damages including carcinogens can also cause the collapse of chemo-surveillance to result in the evolution of CSCs of cancer. Maintenance of the functionality of chemo-surveillance is the top priority to stay away from cancer, and to put cancer away if it has evolved.

War on Cancer Can Never Be Won if the Therapy Is Following the Course Failing to Heal the Wound

Curing cancer was considered a monumental national honor, so President Nixon declared "war on cancer" in 1971 as a presidential project trying to accomplish that great honor in 5 years [15]. Health profession failed the challenge during the intensive presidential support and is still failing 50 years later as cancer mortalities remain at old time high. Destruction to kill cancer cells was the major strategy used in the past to combat cancer. Destruction is inappropriate for the therapy of cancer arising as a consequence of wound not healing properly. The functionality of chemo-surveillance has been badly damaged for cancer to manifest clinical symptom. Destruction creates more wounds to aggravate the already bad situation. So even the therapy is successful to achieve complete remission. It is just the beginning of the contest of the restoration of functionality of chemo-surveillance and the proliferation of CSCs which are not responding to destruction therapy. If the restoration of the functionality of chemo-surveillance prevails, it is then a real success of cancer therapy. The restored chemo-surveillance can subdue CSCs not taken out by the destruction therapy [16]. Most likely only the early-stage cancer patients whose functionality of chemo-surveillance has not been fatally damaged can be saved. If the functionality of chemo-surveillance has been fatally damaged, then the proliferation of CSCs is likely to prevail to result in the recurrence which is always fatal. So only a very small early-stage cancer patients benefit from destruction therapy, while the majority of cancer patients succumb to the therapy. Cancer mortalities reflect the failure of destruction therapy in the past to save the majority of cancer patients. There is an urgent need to modify destruction therapy to save cancer patients. Modifications to implement the agents capable to eradicate CSCs and to restore the functionality of chemo-surveillance are essential for the success of destruction therapy to put cancer away [4,10,17,18].

War on Cancer Can Be Easily Won, If the Therapy Is Following the Course Successfully Healing the Wound

Healing wound is not a big deal if the functionality of chemo-surveillance is intact, just to let the nature to take its course to heal the wound. Curing cancer is also not a big deal, if the therapy is following the course successfully healing the wound. The key is to restore the functionality of chemo-surveillance by the administration of DIs and DHIs, and to plug the leakage of renal tubules with phenylacetylglutamine to prevent excessive urinary excretion of wound healing metabolites. The employment of wound healing metabolites to target PSCs and CSCs is an excellent choice because healing wound is a major biological mission of these cells. Naturally, wound healing metabolites are readily accepted into these cells protected by drug resistant mechanism. CSCs are now considered a primary cause of treatment failure. Many biological characteristics that enable cancer progression are attributable to CSCs, including angiogenesis, metastasis, and drug resistance. The success of cancer therapy depends greatly on the eradication of CSCs. CSCs normally reside dormant in acidic and hypoxic microenvironment hard to reach by the blood. Big molecules such as monoclonal antibodies and interference RNA against the expression of telomerase were vigorously pursued in the past to target CSCs but failed in clinical trials. Big molecules cannot access CSCs to achieve therapeutic effect. The discovery of drugs effective against CSCs is very urgent. Wound healing metabolites, which are mostly small molecules easily diffusible, are the best hope to eradicate CSCs. In fact, CDA-2 has demonstrated clinical efficacy against Myelodysplastic Syndrome (MDS), which is a disease attributable entirely to CSCs [19]. CDA-2 is a preparation of wound healing metabolites purified from freshly collected urine [9]. CDA-2 has been approved for the therapy of MDS by the Chinese FDA in 2017 [20,21].

Abnormal MEs are the target of wound healing metabolites to terminate unnecessary proliferation of PSCs and CSCs as well as cancer cells. Abnormal MEs are an excellent therapeutic target, because these abnormal MEs are very critical for the evolution of CSCs and maintenance of malignant growth. MEs play an important role on the regulation of cell replication and differentiation. DNA methylation controls the expression of tissue specific genes [22], and pre-rRNA ribose methylation controls the production of ribosome [23], which in turn dictates the commitment of cells to initiate replication [24]. The association with telomerase turns MEs to become abnormal [5], which alters Km values of the tumor isozyme pair of methionine adenosyl transferase-S-adenosylhomocysteine hydrolase to increase 7-fold higher than the normal isozyme pair [25, 26]. The increased Km values enable cancer cells to hold a larger pool sizes of S-adenosylmethionine and S-adenosylhomocysteine important to maintain the stability of MEs and to carry on malignant growth [27,28]. Abnormal MEs are responsible for the blockade of differentiation of cancer cells to perpetuate malignant growth, and destabilization of abnormal MEs terminate malignant growth to direct cancer cells to become terminally differentiated cells unable to replicate. Abnormal MEs are the top therapeutic target because they are common to all PSCs, CSCs, and cancer cells. A stroke to eliminate abnormal MEs can also eliminate almost all problems related to wound healing and cancer. Afterall cancer is a disease contributed by multiple issues such as membrane hyperpermeability, chemo-surveillance, blockade of differentiation, and activation of oncogenes or inactivation of suppressor genes. Among these various issues, blockade of differentiation stands out as the most important one, because

when this issue is solved, all other issues will also be solved. We are using wound healing metabolites to put out abnormal MEs that can also restore chemo-surveillance. When the functionality of chemo-surveillance is restored, the issue of membrane hyperpermeability will be gone due to the loss of origin to stir up inflammatory response. The issues of oncogenes and suppressor genes can also be set aside. Afterall, oncogenes and suppressor genes are cell cycle regulatory genes. When cells are in cell cycle replicating, these genes play very important roles. But if cells exist cell cycle to undergo TD, these genes have no roles to play. So, induction of TD is an easy way to solve gene abnormalities which are otherwise very difficult problems to solve. Even one gene abnormality is brilliantly solved, there may pop up another gene abnormality to cause difficult cancer problem. It is an endless struggle to solve gene abnormalities. Therefore, destabilization of abnormal MEs is the best to take care of cancer. There remains a big problem. The tumor mass will not go away. The survival tumor mass is harmless, but it remains a fearful concern. We must come up a different criterion for the evaluation of therapeutic efficacy of differentiation therapy. Disappearance of circulating cancer cells and CSCs can be a valid therapeutic endpoint. Quantitative assessment of the functionality of chemo-surveillance may also serve as a valid therapeutic endpoint.

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