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Opinion

Eradication of Cancer Stem Cells to Win the War on Cancer

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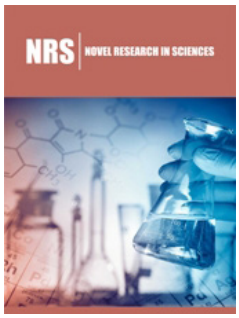

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Opinion

War on cancer

War on cancer was the third presidential project declared by President Nixon in 1971 [1]. A presidential project is either to solve a catastrophic national crisis such as the Manhattan Project of President Roosevelt to develop atomic bomb to finish World War II, or to establish a monumental national honor such as the Apollo project of President Kennedy to send people to moon and back. Apparently, President Nixon considered solution of cancer a monumental national honor to declare war on cancer as his presidential project. Health profession failed the challenge to put cancer away during the 5 years of intensive presidential support, and the following 45 years of entire national support allocated to cancer. Actually, war on cancer can be easily won if the battle is conducted following the course of successful wound healing [2-4]. It can also never be won if the battle is conducted following the course that fails to heal the wound [2-4]. Wound healing and the evolution of cancer are closely related to involve progenitor stem cells as the critical common elements. Healing wound is not a big deal. Wounds are always successfully healed without having to put up any effort, just to let the nature to do the healing. Medications such as suture and antibiotics are subsidiary to speed up the healing or to prevent infection. If chemo-surveillance is intact such as healthy people that can provide enough wound healing metabolites functioning as Differentiation Inducers (DIs) and Differentiation Helper Inducers (DHIs) [5], then a spike of prostaglandins, which are very active DIs produced in response to wound [6], can promote perfect wound healing to avoid cancer. But if chemo-surveillance has been compromised due to pathological conditions that prompt the production of tumor necrosis factor to cause damage of chemo-surveillance such as cancer patients, then wound created by destructive agents cannot be healed, and instead can lead to the proliferation of Cancer Stem Cells (CSCs) and Progenitor Stem Cells (PSCs) to make the situation worse. Evidently chemo-surveillance plays an important role to determine the success of cancer therapy. Cancer therapy that protects chemo-surveillance is likely to win the war on cancer and cancer therapy that destroys chemo-surveillance is likely to fail the challenge to win the war on cancer.

Wound healing metabolites are the best hope to win the war on cancer

Destabilization of abnormal Methylation Enzymes (MEs) through DIs and DHIs is the critical mechanism to promote Terminal Differentiation (TD) of PSCs to successfully healing the wound. PSCs are protected by ATP binding cassette drug pumps [7], which are not blocking the uptake of wound healing metabolites. CSCs, being originated from PSCs, are also protected by ATP binding cassette drug pumps [8,9]. Apparently wound healing metabolites are the pharmacological agents most suitable for the therapy of CSCs. Destabilization of abnormal MEs then is the most effective weapon to eradicate CSCs. At present, Cell Differentiation Agent (CDA) formulations are the only cancer drugs to display effectiveness against CSCs, which are the most likely cancer drugs to win the war on cancer [10,11]. CDA formulations are indeed the most appropriate cancer drugs for the therapy of cancer arising as a consequence of wound not healing properly [3].

The therapeutic endpoint of CDA formulations is the TD of cancer cells. Disappearance of the tumor mass definitely is not a valid endpoint for the evaluation of the therapeutic efficacy of CDA formulations. Disappearance of cancer cells is the therapeutic endpoint of hematological cancers, which can also be used as the endpoint for the evaluation of CDA formulations against hematological cancers. The disappearance of circulating cancer cells may be a valid endpoint for the evaluation of therapeutic efficacy of CDA formulations against solid tumors. If surviving tumor mass is a fearful concern, surgical removal may be a perfect combination. Surgery to remove surviving tumor mass can eliminate fearful concern, and the application of CDA formulations can assure quick recovery of the surgical wound and the prevention of possible metastasis. Treatment alternately with cytotoxic chemotherapy may be another winning combination, relying on cytotoxic drugs to eliminate tumor mass and CDA formulations to eradicate CSCs and to restore chemo-surveillance. Cytotoxic chemotherapy is the choice of cancer establishments to combat cancer in the past but fails to win the battle. Actually, cytotoxic drugs are inappropriate for the therapy of cancer arising as a consequence of wound not healing properly, because they create more wounds to aggravate the already bad situation. Cytotoxic chemotherapy is following the wound healing course that fail to heal the wound, and instead to create more cancer. The destruction of chemo-surveillance and the inability to put away CSCs are the reasons cytotoxic chemotherapy fails to win the war on cancer. Of course, cytotoxic chemotherapy can cure early stage cancer if chemo-surveillance is not fatally damaged in the process. The recovery of chemo-surveillance can take care of CSCs not eliminated by the treatment. But if chemo-surveillance is fatally damaged, the recurrence and the fatality are the inevitable consequences. CDA formulations can be used to remedy the grave adverse effects of cytotoxic drugs. The combination may prove to be successful to win the war on cancer.

The combination with immunotherapy may be another winning combination. CSCs are PSCs minus TET-1 enzyme [12]. The immunogenicity of CSCs is almost the same as that of PSCs, which is tolerable to immune system. So even a successful immunotherapy is developed for cancer treatment, it may need CDA formulations to subdue CSCs. CSCs are the most critical issue of cancer. They are the initiator of the tumor. They are the source of most difficult problems of cancer such as metastasis, recurrence, and drug resistance. CSCs are actually the most critical battle ground of cancer therapy. Cancer drugs effective against CSCs must be considered the most important cancer drugs [13].

Abnormal MEs as the best therapeutic target to win the war on cancer

Destructive strategies have dominated cancer therapy in the past, but are unable to put cancer away [2,3]. Cancer mortalities remain at old time high worldwide. To win the war on cancer, other strategies must be taken into consideration to replace or to modify destruction strategies in order to defeat cancer. Non-destruction strategies effective for cancer therapy include differentiation therapy, hormone therapy, targeted therapy against growth signals, and gene therapy. All of which, except gene therapy, appear to target on abnormal MEs to achieve therapeutic efficacy. Therefore, abnormal MEs are a good target for cancer therapy and an exceptionally good target for CSCs, since toxic therapeutic agents cannot enter CSCs. MEs play a critical role on the regulation of cell replication and differentiation. DNA methylation controls the expression of tissue specific genes [14], and pre-rRNA ribose methylation controls the production of ribosome [15], which in turn dictates the commitment of cells to initiate replication [16]. Biological methylation is mediated by a ternary enzyme complex consisting of Methionine Adenosyl Transferase (MAT)-Methyl Transferase (MT)-S-Adenosyl Homocysteine Hydrolase (SAHH) [17]. SAHH is a steroid hormone receptor, very responsive to steroid hormones and other growth factors. Cells expressing telomerase turn MEs to become exceptionally stable and active to block differentiation [18]. The abnormal MAT-SAHH isozyme pair display K_m values 7-fold higher than the normal isozyme pair [17,19]. When cancer cells are induced to undergo TD, the pool sizes of s-adenosylmethionine and S-adenosylhomocysteine shrink greatly [20], and the K_m values of the cancer MAT-SAHH isozyme pair revert back to those of normal isozyme pair [21]. Thus, abnormal MEs play an important role on the initiation and the maintenance of malignant status. Chemo-surveillance is implemented to keep cells with abnormal MEs to buildup to evolve into cancer cells. If cancer cells have evolved, the best solution is to eliminate abnormal MEs to put cancer cells away.

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