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Opinion

It Has Been Half a Century Since President Nixon Declared War on Cancer: Destabilization of Abnormal Methylation Enzymes Has the Blessing of the Nature to Win the War on Cancer

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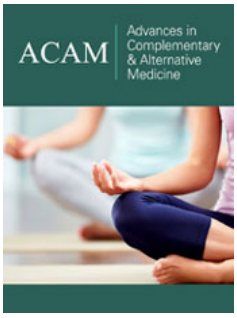

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Introduction

President Nixon declared war on cancer in 1971. When a president of the USA declares a presidential project, he has the determination to achieve the goal in 5 years. There were two precedents: the Manhattan Project of President Roosevelt and the Apollo Project of President Kennedy. In both precedents, nuclear physicists and rocket engineers were successful to achieve the presidential project within 5 years. Health profession failed the challenge during the 5 years of intensive presidential support, and in the following 44 years of earnest public expectation. Is it so difficult to put cancer away? Yes, as we have pointed out previously [1], that in theory it was not possible to solve cancer with conventional cell killing strategies, because cancer stem cells (CSCs) stood in the way. And no, there were other ways to get rid of CSCs and to solve problems confronting cancer [2,3].

Maintenance of the Integrity of Cell Membrane and Chemo-surveillance Plays a Magnificent Role to Keep Cancer Away

The progression from healthy persons through myelodysplastic syndrome (MDS) to acute myeloid leukemia is a classic model of human cancer evolution. Immunological disorders are the triggering causes of MDS. In other cases of cancer, the triggering causes can be toxic chemicals such as carcinogens that cause mutations. Humans produce defensive cytokines in response to triggering causes, which lead to the destruction of terminal stage stem cells and the membrane integrity. Progenitor stem cells (PSCs) then proliferate to replenish the depleted terminal stage stem cells. Repairing the damage is an important biological mission of PSCs. Under normal healthy state, PCSs respond to the damage signal to proliferate and are quickly induced to undergo terminal differentiation (TD) by surveillance chemicals after completion of the repair. In the unhealthy state of long term of immunological disorders or exposure to toxic carcinogens, surveillance chemicals are depleted due to excessive urinary excretion caused by cytokine damage of the cell membrane permeability [4,5]. Without sufficient surveillance chemicals, PSCs keep on proliferating, and may accidently introduce methyl groups at the promoter site of TET-1 enzyme to silence the expression of this enzyme. When this happens, PSCs become CSCs. PSCs express telomerase like most cancer cells to lock methylation enzymes (MEs) in exceptionally stable and active state to block differentiation [6,7]. PSCs are still able to carry out differentiation programs, relying on TET enzymes to achieve DNA hypomethylation. When TET-1 is silenced, the differentiation capacity is completely lost. Surveillance chemicals become the essential defense to prevent the buildup of CSCs and their progression to more rapidly replicating progenies. It is obvious that the integrity of membrane permeability and chemo-surveillance is very important to protect healthy persons from becoming cancer patients. The association of telomerase with MEs and the silence of TET-1 represent the first hit and the second hit of the two hits carcinogenesis theory advocated by Knudson [8].

Destabilization of Abnormal MEs Has the Nature's Blessing to Win the War on Cancer

Destabilization of abnormal MEs results in TD to terminate malignant growth. Activation of oncogenes and inactivation of suppressor genes play important role to promote malignant growth when differentiation is blocked by abnormal MEs and the silencing of TET-1. TD can negate the contribution of oncogenes and suppressor genes. Cell killing strategies using toxic chemicals and radiation also can negate the contribution oncogenes and suppressor genes. Both are effective to stop malignant growth. Destabilization of abnormal MEs is a better choice, because it does not induce aberrant hypermethylation, and cause damage to chemo-surveillance. It is actually the nature's prescription via surveillance chemicals to protect healthy persons. Chemo-surveillance is working magnificent well as there are far more healthy people than cancer patients, considering the conversion of PSCs to CSCs is a simple silencing of TET-1 that can easily be accomplished by PSCs. CDA-2, also the nature's prescription to destabilize abnormal MEs has the best therapeutic record of MDS which is a disease attributable entirely to CSCs [9,10]. ATRA plus As_2O_3, a combination of differentiation inducer (DI) and differentiation helper inducer (DHI), is the standard therapy of acute promyelocytic leukemia [11]. Imatinib, a DHI, is the standard therapy of chronic myeloid leukemia [12]. A combination of phenylbutyrate and signal transduction inhibitors, namely a combination of DHIs, is very effective on untreatable glioblastoma [13]. It is apparent, the clinical evidence shows that destabilization of abnormal MEs can win the war on cancer.

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