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Opinion

Think Hard on the Destabilization of Abnormal Methylation Enzymes to Combat Cancer: It Can be Life Saving

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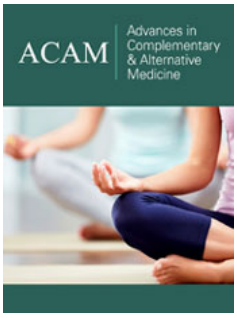

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Abnormal Methylation Enzymes (MEs) are an Important Issue of Cancer

Biological methylation is mediated by a ternary enzyme complex consisting of methionine adenosyl-transferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH). SAHH is a steroid receptor. Steroid factors generated by growth signals play dominant roles on the regulation of normal MEs. Cancer MEs are abnormal due to association of MAT with telomerase which becomes a dominant factor to regulate cancer MEs. The association of cancer MEs with telomerase locks cancer MEs in an exceptionally stable and active state so that hypomethylation of DNA necessary for the activation of differentiation related genes cannot take place. Blockade of differentiation attributable to abnormal MEs is a very important issue of cancer. Because of the blockade of differentiation, cancer cells keep on replicating, allowing oncogenes and suppressor genes to attract a great deal of attention in the field of cancer. Oncogenes and suppressor genes are cell cycle regulatory genes. They have important roles to play when cells are in cell cycle replicating. But they have no role to play when replicating cells are diverted to undergo terminal differentiation (TD). So, a stroke to destabilize abnormal MEs can wipe out all damages generated by oncogenes and suppressor genes.

Destabilization of Abnormal MEs is Very Effective for Cancer Therapy

All-trans-retinoic acid (ATRA) plus As_2O_3 and imatinib mesylate are standard therapies for acute promyelocytic leukemia and chronic myeloid leukemia. Complete remissions are above 90%, and the remission can be very long. Therapy as such must be considered as the best cancer therapy achieved. ATRA is a differentiation inducer (DI) which is a chemical capable of eliminating telomerase from abnormal MEs. As_2O_3 and imatinib mesylate are differentiation helper inducers (DHIs) which are inhibitors of individual enzymes of MEs. DHIs alone at very high concentrations can also induce TD. DHIs when employed at concentrations not effective to induce TD can greatly potentiate the activity of DIs to induce TD. DIs are better inducers of TD. But DIs alone cannot push all cancer cells to undergo TD. 95% is the highest extent of TD that can be achieved by a DI alone, In the presence of a DHI, the extent of TD can be pushed to 100%. This is because DI alone can turn MEs to become nucleases causing damage to prevent the completion of TD. The conversion of MEs to nucleases can be prevented by a DHI. Therefore, it is essential to formulate DI and DHI together to make a perfect drug to target abnormal MEs.

Destabilization of Abnormal MEs as the Nature's Choice to Combat Cancer

In 1987, Liau MC et al. introduced the concept of chemo surveillance as a natural defense mechanism against cancer. This hypothesis was based on the observation that healthy people could maintain a steady level of hydrophobic metabolites in their plasma, whereas cancer patients tended to show deficiency of such metabolites due to excessive urinary excretion. Among such metabolites were chemicals active as DIs and DHIs. The implication is that healthy people have enough DIs and DHIs in their circulation to keep a check on the evolution

of cancer cells, whereas in cancer patients a lack of DIs and DHIs depresses their ability to stop the evolution of cancer cells. The evolution of cancer in the case of myelodysplastic syndrome (MDS) strongly supports the validity of this hypothesis.

MDS often starts with a display of an immunological disorder, which prompts the local production of inflammatory cytokines. Among such cytokines, tumor necrosis factor (TNF) is the critical factor related to the development of MDS. It causes excessive apoptosis of bone marrow stem cells, thus severely affecting the ability of the patient to produce hematopoietic cells such as erythrocytes, platelets, and neutrophils. TNF is also named cachectin, because of its causation of cachexia, a syndrome commonly shared by inflammatory and cancer patients. A characteristic disorder of cachexia is the excessive urinary excretion of low molecular weight metabolites because of vascular hyperpermeability caused by TNF. As a consequence, chemo surveillance normally operating in healthy people to keep progenitor stem cells in check becomes dysfunctional, allowing progenitor stem cells to build up in order to replenish unipotent stem cells wiped out by TNF. During the course of MDS progression, mutations affecting the enzyme functions of Tet 2 and other enzymes are frequently observed, which may play significant roles on the evolution of progenitor stem cells to become cancer stem cells (CSCs). As anemia in MDS patients becomes worse, chromosomal abnormalities such as translocations and deletions characteristic of cancer cells arise eventually pushing MDS patients to progress to acute myeloid leukemia.

CDA-2 is very good for the therapy of MDS, which is a collection of DIs and DHIs purified from urine. MDS is a disease attributable entirely to CSCs. Therefore, drugs effective to destabilize abnormal MEs are definitely effective against CSCs which are not responsive to cytotoxic drugs neither radiation. Destabilization of abnormal MEs is, therefore, an ideal strategy to target both cancer cells and CSCs.