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Opinion

Membrane Hyperpermeability is a Very Important Issue of Cancer

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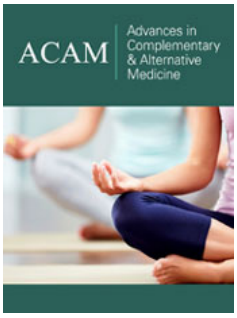

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Membrane Hyperpermeability is a Critical Event for Cancer Cells to Emerge

As previously reported [1], cancer stem cells (CSCs) are thought to originate from progenitor stem cells (PSCs) based on cell features and biological missions. PSCs are stem cells which have sustained one of the two hits required for transformation according to the Knudson hypothesis [2]. Thus, PSCs are literally semi-CSCs. The first hit can be overexpression of telomerase, which becomes associated with methylation enzymes (MEs) to lock these enzymes in an exceptionally stable and active state, leading to DNA hypermethylation and a block in expression of cell differentiation genes. PSCs are still able to carry out some differentiation programs, relying on TET enzymes to reverse DNA hypermethylation [3]. The second hit is knock out of TET enzymes, eliminating the differentiation capability of PSCs, promoting semi-CSCs to become genuine CSCs. TET-1 of cancer cells is often inactivated by silencing, and TET2 is inactivated by mutation [4-6]. TET1 preferentially acts on the 5-methylcytosine (5mC) located at the gene promoter site, whereas TET2 preferentially acts on the 5mC located in the gene body. The effect of 5mC in the gene promoter site is an all or none effect on gene expression, whereas the effect of 5mC in the gene body influences the extent of gene expression. Therefore, the silencing of TET1 is a more critical event, which can be easily accomplished in PSCs which have very active MEs. The conversion of PSCs to CSCs is very easy without the help of carcinogens. Of course, carcinogens have important roles to activate oncogenes or to inactivate suppressor genes, which are commonly involved in cancer progression.

The replication of cells with abnormal MEs, such as PSCs and cancer cells, is under close surveillance in healthy persons. If not, the incidence of cancer in young people would be skyrocketing. Healthy persons produce a steady level of metabolites active as differentiation inducers [DIs] and differentiation helper inducers (DHIs) to prevent the evolution of cancer [7]. The conversion of PSCs to CSCs may be taking place frequently. CSCs in healthy persons can be effectively induced to undergo terminal differentiation by endogenous DIs and DHIs. The problem arises when such metabolites cannot be kept in the body due to changes in membrane permeability. Carcinogenesis experiments often proceed from a brief initiation with carcinogens, followed by long term promotion with inflammatory agents which cause membrane hyperpermeability, leading to loss of endogenous metabolites inhibitory to the replication of cancer cells. Infections have the same effect as inflammatory agents to cause membrane hyperpermeability. Acute infection is only temporary, which does not have an impact on cancer. Chronic infections, such as HIV, HBV, HCV, and HPV, are frequently associated with the occurrence of cancer.

Elimination of Membrane Hyperpermeability is Very Helpful for the Prevention and Therapy of Cancer

Myelodysplastic syndrome (MDS) is a classic case that illustrates the role of membrane hyperpermeability in the evolution of cancer. 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 [8]. 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 terminal cancer patients. A characteristic disorder of cachexia is the excessive urinary excretion of low molecular weight metabolites because of vascular hyperpermeability caused by TNF [9,10]. As a consequence, chemo-surveillance normally operating in healthy persons to keep PSCs in check becomes dysfunctional, allowing PSCs to build up in order to replenish unipotent stem cells wiped out by TNF. Subsequent loss of TET enzymes causes progression of PSCs into CSCs. Silencing of DNA repair programs causes further progression at the chromosomal level, enabling abnormalities such as translocations and deletion that eventually push MDS patients to become acute myeloid leukemia patients [11]. Antibody of TNF is very effective to halt the progression of MDS if given at the early stage of the disease [8].

Phenylacetylglutamine is inactive as DI or DHI. It is, however, effective to fix membrane hyperpermeability, and to prevent excessive urinary excretion of low molecular weight metabolites of the cancer patient [7]. By keeping chemo-surveillance intact, phenylacetylglutamine was found effective to prevent chemical hepatocarcinogenesis [12], and to show good therapeutic effect on early stage cancers [7]. Cytotoxic chemotherapy, on the other hand, progressively increased patient's urinary excretion of low molecular weight metabolites [7]. The cytotoxic destruction of cancer cells is like inflammatory effect to contribute to membrane hyperpermeability, resulting in the breakdown of chemo-surveillance. The patient eventually become defenseless against cancer. So, recurrence is inevitable, because chemotherapy cannot eliminate CSCs. Anti-cachexia chemicals such as phenylacetylglutamine effective to stop leakage of membrane is very helpful for the prevention and therapy of cancer.

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