

# Restoration of the Chemo-surveillance Capability is Essential for the Success of Chemotherapy and Radiotherapy to Put Cancer Away

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## Opinion

### Chemo-surveillance is an Important Mechanism to Protect Healthy People from Becoming Cancer Patients.

Chemo-surveillance was introduced by Liao et al. [1] in 1987, which was an important finding but unfortunately did not attract attention. As previously stated, [2] the evolution of cancer in the case of myeloid dysplastic syndrome (MDS) strongly supported the validity of this hypothesis. The evolution of cancer in MDS is a classic case of cancer evolution triggered by immunological disorders. Immunological disorders caused by infectious agents such as AIDS, HBV, HCV, HPV, or genetic defects such as severe combined immunodeficiency can lead to cancer. However, the breakdown of immuno-surveillance as the cause of cancer is a misconception. The breakdown of immuno-surveillance prompts the patient to produce high levels of Tumor Necrosis Factor (TNF), which is responsible for the destruction of bone marrow stem cells and the loss of endogenous chemo-surveillance chemicals due to vascular hyperpermeability caused by TNF. The breakdown of chemo-surveillance is ultimately responsible for the build-up of progenitor stem cells to evolve into cancer stem cells (CSCs).

Progenitor stem cells express high levels of telomerase, as do most cancer cells. Methylation enzymes of telomerase expressing cells are abnormal due to their direct association with telomerase [3]. Telomerase complex formation with methylation enzymes locks these enzymes into an extremely stable and active state, suppressing the hypomethylation of DNA necessary for the expression of differentiation related genes. The promoters of differentiation related genes in stem cells are silenced by DNA methylation, which must be removed for the genes to be re-expressed. Most cancer cells over express telomerase, which may result from mutation representing the first hit of the two-hit theory of carcinogenesis advocated by Knudson [4]. Therefore, progenitor stem cells are the normal stem cells sustaining the first hit. A subsequent second hit to inactivate Tet enzymes eventually converts progenitor stem cells to become genuine CSCs. Progenitor stem cells are literally semi-CSCs.

Key metabolites function in chemo-surveillance as differentiation inducers (DIs) and differentiation helper inducers (DHIs), which can effectively keep progenitor stem cells from building up to evolve into CSCs such as the case of MDS. An analogous process can occur via chemical carcinogen induced hepatocarcinogenesis, which proceeds through a schedule very similar to the immunological disorder triggered MDS above described. The initial phase of chemical carcinogenesis, like the immunological disorder of MDS, results from damage to hepatic stem cells, triggering an inflammatory response that leads to clearance of DI and DHI molecules via "leaky" renal excretion, breaking down chemo-surveillance. This is followed by the build-up of progenitor stem cells. Multiple small sized preneoplastic hyperplastic nodules develop during hepatocarcinogenesis which may represent the build-up of progenitor stem cells, because we have detected abnormal methylation enzymes to function actively in these preneoplastic nodules [5]. Most of these preneoplastic nodules disappear later, replaced by a few larger size carcinomas. Phenylacetylglutamine is inactive as DI or DHI. It is, however, effective to prevent the excessive loss of endogenous DIs and DHIs frequently

observed in cancer patients. By keeping chemo-surveillance intact, phenylacetylglutamine was found effective to prevent chemical hepatocarcinogenesis [6], and to have good therapeutic effect on early stage cancer [1].

### **Restoration of Chemo-Surveillance Capability is Essential for the Success of Chemotherapy and Radiotherapy to Put Cancer Away**

In theory, it is not possible to cure cancer using cytotoxic drugs or radiation, because CSCs stand in the way. Many biological characteristics that enable cancer progression are attributable to CSCs, including angiogenesis, metastasis, and drug resistance. CSCs are resistant to cytotoxic drugs and radiation because these cells overexpress ATP-binding cassette drug pumps that effectively exclude cytotoxic drugs and have activation of anti-apoptosis programs that negate the pro-apoptotic signals activated by DNA damaging agents. CSCs share much in common with progenitor stem cells with respect to cell features and biological mission.

Their biological mission is to repair and to meet the replacement needs of the organ or tissue. When cancer cells are destroyed by cytotoxic drugs or radiation, CSCs proliferate to replace the dead cancer cells, eventually CSCs become the dominant tumor component. Therefore, successful cancer therapy must rely on the elimination of not only cancer cells, but also the subpopulation of CSCs. CSCs are responsive to the induction of differentiation by DI's and DHI's. Restoration of chemo-surveillance capability by DI's and DHI's becomes very important for the successful therapy of cancer. At the early stage, the erosion of chemo-surveillance is not

very severe, and the elimination of the source of erosion, namely cancer cells, may be enough to allow recovery. But in the advanced stage, depletion of endogenous DIs and DHIs is very severe, so that supplements are necessary to restore the function of chemo-surveillance. We have offered cell differentiation agent (CDA) formulations to restore chemo-surveillance capability [7]. It is up to the cancer-treatment establishment to accept our conceptual framework to put cancer away.

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