Anticancer effects of retinoic acid and arsenic trioxide: The other side of the moon

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Abstract:

It was proposed that carcinogenesis can be resulted from the local buildup of strong acids such as HCl. Cancer cells may overproduce weak or moderate organic acids such as oxalate to counteract strong acids, whereas insoluble and rigid calcium oxalate causes organ failure and death. Weak acids such as retinoic acid and arsenous acid, can work in a similar fashion and solubilize insoluble salts, therefore boasting cancer-protecting effects.

Keywords: anticancer effect; retinoic acid; arsenic trioxide; mechanism; arsenous acid

It has been postulated that the local buildup of strong acids such as HCl, mediated by hydrogen bond donors and acceptors and basic amino acids, triggers carcinogenesis^{1,2}. Cancer cells may overproduce organic acids such as oxalate to antagonize HCl, and subsequent formation of insoluble and rigid salts such as calcium oxalate is stressful to cells. Retinoic acid and arsenous acid as weak acids can counteract strong acids directly for cancer protection.

Vitamin A, also known as retinol, is a type of fat-soluble vitamin with similar structure to carotene, including vitamin A1 and vitamin A2. It is first oxidized into retinal in the body and then further oxidized into retinoic acid. It has been noticed that the content of retinoic acid is closely related to tumor cell proliferation since the 1920s. After a long-time study, it has been found that retinoid compounds have effects on inducing differentiation and chemoprophylaxis. Extensive research has indicated that the regulation of gene expression by retinoic acid is direct rather than the result of inhibition of cell proliferation. In the cell, the C-myc gene encodes a DNA binding protein and initiates cell proliferation with growth factors. In vitro experiments have shown that retinoic acid can reduce the expression of C-myc and at the same time increase the expression of CDKs inhibitor P27, thereby inducing the differentiation and apoptosis of small cell lung cancer cells³. Retinoic acid also inhibits the activity of telomerase⁴, and telomerase is a specific marker of tumor cells.

Early in 1996, there was a report about arsenic trioxide in the treatment of leukemia⁵. After emergence of the chemical formulation of arsenic trioxide ATO, it was approved by the US FDA (Trisenox®) for the treatment of acute pro-myelocytic leukemia (APL) in 2000⁶. APL is a unique subtype of acute myeloid leukemia, which is characterized by a specific chromosome translocation t(15;17) and the expression of PML-RAR α fusion protein, which can block cell differentiation and inhibit apoptosis⁷. Arsenic Trioxide is dissolved in saline and administered as a dilute solution of aqueous arsenous acid, and previous study in vitro suggested that arsenic trioxide can induce apoptosis in NB4 cell line (a cell line with typical APL characteristics) and retinoic acid resistant APL cell line^{8,9}. Arsenic trioxide induces molecular remission and prolongs survival in a high proportion of APL patients when used as a single agent¹⁰, and it can also act synergistically with ATRA (all trans retinoic acid)¹¹ to induce degradation of an oncoprotein that drives APL. Both arsenic trioxide and ATRA have the characteristic of degrading PML-RAR α protein, but arsenic trioxide targets the PML moiety of PML-RAR α protein where it can induce sumoylation of specific cysteine residues and stimulate proteasome-mediated degradation of the oncoprotein, while ATRA targets the RAR α moiety of PML/RAR α ¹². Therefore, there is no competition between arsenic trioxide and ATRA. In vitro study suggested that the combined effect of arsenic trioxide and ATRA on NB4-As cells has shown faster differentiation or apoptosis than arsenic trioxide or ATRA alone¹³.

In summary, weak acids can have huge benefit in the fight against cancer.¹⁴⁻¹⁸

Conflict of interest statement

The authors declare no conflict of interests.

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