Molecular pathways in induction of cancer cell apoptosis by Vitamin E analogues

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In Editorial on free radicals and cancer (1) it is postulated that many tumor cells are in pro-oxidant status that results either from increased production of oxygen free radicals or decreased expression of antioxidant enzymes. Possible protective and anticancer activities of antioxidant molecules by scavenging excess of free radicals are complex due to their potential interferences with redox regulation of some important physiological processes e.g. apoptosis. Modulation of the oxidant/anti-oxidant balance towards a more reduced state is likely to have control influence by limiting the survival and invasion of the most cancer cells. Therefore, the systemic administration of low molecular antioxidants could be helpful in the management of the systemic effects as well as for the side effects of therapy in breast cancer patients (2). Some possible protective effect of Vitamin E in cancer treatment have been found (3,4) but more specific effects are attributed to Vitamin E analogs, „mitocans," a novel group of anticancer agents (5).

Vitamin E analogue, alpha-tocopheryl succinate, suppresses malignant mesotelioma in a preclinical model, alters cell cycle distribution sensitizing human osteosarcoma cells to methotrexate-induced apoptosis, promotes breast cancer tumor dormancy, and selectively induces apoptosis in neuroblastoma cells. Mechanisms of such alpha-tocopheryl succinate effects on tumor cells are under intensive investigation. Alpha-tocopheryl succinate-induced apoptosis may proceed through different mechanisms such as modulation of ERK1/2 and c-Jun N-terminal kinase in a biphasic manner (6), or by tocopherol-associated protein-1 (7). It seems that mitochondria play a central role in apoptosis induced by alpha-tocopheryl succinate indicating a role of reactive oxygen species (ROS) in apoptosis induction. Molecular mechanism of alpha-tocopheryl succinate-induced apoptosis in cancer cells emphasizes the multiple roles of reactive oxygen species and Bcl-2 family proteins. A role of nitric oxide and superoxide after alpha-tocopheryl succinate application in apoptotic and anticancer effects are also examined (8). These results, in some aspects, are opposite to those recently postulated (5) that it is essential for alpha-tocopheryl succinate to be redox-silent.

In this volume in a paper *Alpha-tocopheryl succinate (α-TOS) influences cell vitality and enzyme activity in Ehrlich ascites carcinoma cells*, by Karmen Stankov et al (9), a new original data are presented which may be useful in detection of molecular mechanism of alpha-tocopheryl succinate action. Authors investigated the *in vivo* effects of intraperitoneal application α-TOS on vitality of Ehrlich ascites carcinoma cells (EAC) (in mice), as well as the influence of α-TOS on specific activity of enzymes involved in antioxidative mechanisms in EAC cells. The observed decrease in antioxidative potential (decrease in glutathione-dependent enzyme activity), may have the important influence on EAC cells increased susceptibility towards apoptosis, that was shown by decreased vitality of EAC cells after intraperitoneal application of α-TOS.

These changes in enzyme activity might be due to the alterations in gene expression, possibly induced by the α-TOS influence on ROS production or other signal transduction mechanisms. The vitamin E analogs inhibit proliferation of cancer cells by several mechanisms including inhibition of DNA synthesis and by affecting the protein kinase C and the MAP kinase pathways. They are also able to efficiently induce the mechanisms of mitochondrial signal transmission (including ROS generation), which triggers apoptosis. Parallel existence of different mechanisms of action (redox and direct effects of the α-TOS) may be very important for effectiveness of some drugs used in clinical practice.

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