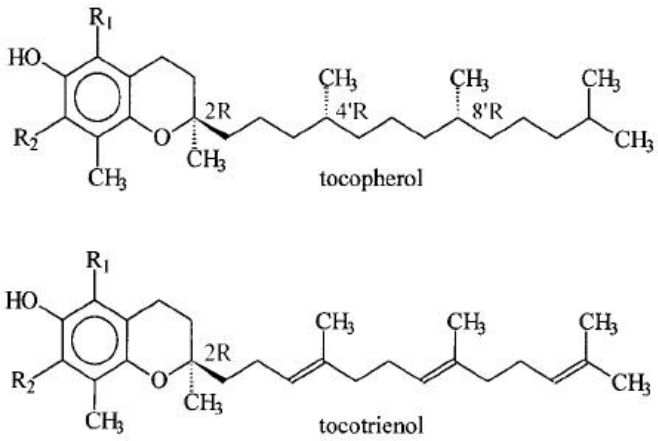
VITAMINA E

IN

MALATTIE LINFOPROLIFERATIVE



R_1	R_2	
CH_3	CH_3	α
CH_3	H	β
H	CH_3	γ
H	H	δ

Struttura chimica di analoghi tocoferoli e tocotrienoli

Introduzione

Le vitamine E naturali includono due gruppi di composti liposolubili strettamente correlati, i tocoferoli e i tocotrienoli, ciascuno con quattro analoghi α, β, γ, δ (Ricciarelli, Zingg et al. 2001; Azzi, Gysin et al. 2003; Hensley, Benaksas et al. 2004). Tali molecole hanno notevoli proprietà anti-ossidanti, proteggendo così le cellule ed i tessuti da radicali liberi (come superossido, ossido nitrico, radicali idrossilici) ed altre specie reattive (come perossido di idrogeno, perossinitrite, acido ipocloroso) (Brigelius-Flohe and Traber 1999; Fang, Yang et al. 2002).

Studi epidemilogici indicano che alti livelli di γ-tocoferolo sono associati ad un ridotto rischio di cancro alla prostata (Jiang, Christen et al. 2001; Huang, Alberg et al. 2003).
Studi in vitro indicano che α-tocoferolo inibisce la crescita di varie linee cellulari tumorali, come:

- Cellule di carcinoma della prostata (Israel, Yu et al. 2000; Yu, Somasundar et al. 2002; Zhang, Ni et al. 2002)
- Cellule di carcinoma del seno (Yu, Israel et al. 1999; Pussinen, Lindner et al. 2000; Yu, Liao et al. 2001)
- Cellule di carcinoma del polmone (Neuzil, Weber et al. 2001)
- Cellule di carcinoma della parotide (Prasad and Kumar 1996)
- Cellule di carcinoma dello stomaco (Rose and McFadden 2001; Wu, Zhao et al. 2002)
- Cellule di carcinoma del colon (Neuzil, Weber et al. 2001)
- Cellule di carcinoma del pancreas (Heisler, Towfigh et al. 2000)
- Cellule di carcinoma squamoso orale (Elattar and Virji 1999)
- Cellule di melanoma (Prasad, Cohrs et al. 1990)
- Cellule di neuroblastoma (Prasad, Kumar et al. 2003)
- Cellule di glioma (Prasad, Kumar et al. 2003)
- Cellule leucemiche (Yamamoto, Tamai et al, 2000)
- Cellule di linfoma (Turley, Funakoshi et al. 1995; Yu, Sanders et al. 1997; Dalen and Neuzil 2003).

I tipi di effetti (differenziamento, inibizione della proliferazione ed apoptosi) dipendono dalla concentrazione di α-tocoferolo, il periodo di trattamento, le condizioni di coltura ed il tipo di cellule tumorali. Concentrazioni basse di α-tocoferolo causano inibizione della proliferazione e differenziamento, mentre concentrazioni più alte inducono apoptosi (Prasad, Kumar et al. 2003).

Anche studi in vivo indicano che α-tocoferolo ha un effetto di soppressione della crescita tumorale (Prasad review). In topi, la somministrazione di α-tocoferolo riduce marcatamente la crescita di cellule tumorali, come ad esempio:

- cellule di carcinoma del seno (Malafa and Neitzel 2000)
- cellule di carcinoma del colon (Prasad, Kumar et al. 2003)
- cellule di melanoma (Malafa, Fokum et al. 2002)
- cellule di neuroblastoma (Prasad, Kumar et al. 2003)
- cellule di linfoma (Sarna, Kumar et al. 2000)

α-Tocoferolo induce anche un potenziamento dell'azione antitumorale di diversi agenti chemioterapici come l'adriamicina, il cisplatino ee il tamoxifen (Ripoll, Rama et al. 1986; Prasad, Hernandez et al. 1994). Inoltre, α-tocoferolo protegge le cellule del midollo osseo contro gli effetti letali della doxorubicina (Fariss, Fortuna et al. 1994). Ciò indica che α-tocoferolo può potenziare l'effetto antitumorale di agenti chemioterapici, proteggendo le cellule normali dagli effetti tossici (Prasad, Kumar et al. 2003).

L'azione antitumorale della vitamina E può esercitarsi anche a livello della disseminazione neoplastica. Infatti diversi lavori indicano un potenziale antiangiogenetico per la vitamina E (Shklar and Schwartz 1996; Tang and Meydani 2001; Neuzil, Kagedal et al. 2002; Inokuchi, Hirokane et al. 2003; Miyazawa, Tsuzuki et al. 2004).

Tutti questi dati indicano che la vitamina E può essere di enorme utilità terapeutica nella prevenzione e nel trattamento delle neoplasie, soprattutto se in combinazione con altre molecole con dimostrata attività antineoplastica.

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Mol Aspects Med. 2003 Dec;24(6):325-36.

The role of alpha-tocopherol in preventing disease: from epidemiology to molecular events.

Azzi A, Gysin R, Kempna P, Ricciarelli R, Villacorta L, Visarius T, Zingg JM.

The function of vitamin E has been attributed to its capacity to protect the organism against the attack of free radicals by acting as a lipid based radical chain breaking molecule. More recently, alternative non-antioxidant functions of vitamin E have been proposed and in particular that of a "gene regulator". Effects of vitamin E have been observed at the level of mRNA or protein and could be consequent to regulation of gene transcription, mRNA stability, protein translation, protein stability and post-translational events. Given the high priority functions assigned to vitamin E, it can be speculated that it would be inefficient to consume it as a radical scavenger. Rather, it would be important to protect vitamin E through a network of cellular antioxidant defences, similarly to what occurs with proteins, nucleic acids and lipids.

FASEB J. 1999 Jul;13(10):1145-55.

Vitamin E: function and metabolism.

Brigelius-Flohe R, Traber MG.

Although vitamin E has been known as an essential nutrient for reproduction since 1922, we are far from understanding the mechanisms of its physiological functions. Vitamin E is the term for a group of tocopherols and tocotrienols, of which alpha-tocopherol has the highest biological activity. Due to the potent antioxidant properties of tocopherols, the impact of alpha-tocopherol in the prevention of chronic diseases believed to be associated with oxidative stress has often been studied, and beneficial effects have been demonstrated. Recent observations that the alpha-tocopherol transfer protein in the liver specifically sorts out RRR-alpha-tocopherol from all incoming tocopherols for incorporation into plasma lipoproteins, and that alpha-tocopherol has signaling functions in vascular smooth muscle cells that cannot be exerted by other forms of tocopherol with similar antioxidative properties, have raised interest in the roles of vitamin E beyond its antioxidative function. Also, gamma-tocopherol might have functions apart from being an antioxidant. It is a nucleophile able to trap electrophilic mutagens in lipophilic compartments and generates a metabolite that facilitates natriuresis. The metabolism of vitamin E is equally unclear. Excess alpha-tocopherol is converted into alpha-CEHC and excreted in the urine. Other tocopherols, like gamma- and delta-tocopherol, are almost quantitatively degraded and excreted in the urine as the corresponding CEHCs. All rac alpha-tocopherol compared to RRR-alpha-tocopherol is preferentially degraded to alpha-CEHC. Thus, there must be a specific, molecular role of RRR-alpha-tocopherol that is regulated by a system that sorts, distributes, and degrades the different forms of vitamin E, but has not yet been identified. In this article we try to summarize current knowledge on the function of vitamin E, with emphasis on its antioxidant vs. other properties, the preference of the organism for RRR-alpha-tocopherol, and its metabolism to CEHCs.

Br J Cancer. 2003 Jan 13;88(1):153-8.

Alpha-tocopheryl succinate sensitises a T lymphoma cell line to TRAIL-induced apoptosis by suppressing NF-kappaB activation.

Dalen H, Neuzil J.

Activation of nuclear factor-kappaB (NF-kappaB) can interfere with induction of apoptosis triggered by the tumour necrosis factor-related apoptosis-inducing ligand (TRAIL; Apo2L). Therefore, agents that suppress NF-kappaB activation may sensitise cells to TRAIL-dependent apoptosis. Exposure of Jurkat cells to TRAIL resulted in massive and saturable apoptosis induction, following an initial lag time. This lag was abolished by pretreatment of the cells with subapoptotic doses of alpha-tocopheryl succinate (alpha-TOS) or the proteasome inhibitor MG132. Exposure of the cells to TRAIL led to a rapid, transient activation of NF-kappaB, a process that was suppressed by cell pretreatment with alpha-TOS or MG132. Activation of NF-kappaB by TNF-alpha prior to TRAIL exposure increased resistance of the cells to TRAIL-mediated apoptosis. We conclude that alpha-TOS sensitises cells to TRAIL killing, at least in some cases, through inhibition of NF-kappaB activation. This further supports the possibility that this semisynthetic analogue of vitamin E is a potential adjuvant in cancer treatment, such as in the case of TRAIL-mediated inhibition of cancer.

Anticancer Res. 1999 Jan-Feb;19(1A):365-8.

Biphasic action of vitamin E on the growth of human oral squamous carcinoma cells.

Elattar TM, Virji AS.

Treatment of human tongue squamous carcinoma cell, SCC-25, with physiological concentrations of vitamin E succinate (VES) which varied from 0.001 to 50 mumoles/L resulted in significant dose-dependent stimulation of cell growth. Whereas, pharmacological doses of the vitamin (100-154 microM) induced significant inhibition in cell growth. The possible anticarcinogenic mechanisms of action of vitamin E are discussed.

Nutrition. 2002 Oct;18(10):872-9.

Free radicals, antioxidants, and nutrition.

Fang YZ, Yang S, Wu G.

Radiation hazards in outer space present an enormous challenge for the biological safety of astronauts. A deleterious effect of radiation is the production of reactive oxygen species, which result in damage to biomolecules (e.g., lipid, protein, amino acids, and DNA). Understanding free radical biology is necessary for designing an optimal nutritional countermeasure against space radiation-induced cytotoxicity. Free radicals (e.g., superoxide, nitric oxide, and hydroxyl radicals) and other reactive species (e.g., hydrogen peroxide, peroxynitrite, and hypochlorous acid) are produced in the body, primarily as a result of aerobic metabolism. Antioxidants (e.g., glutathione, arginine, citrulline, taurine, creatine, selenium, zinc, vitamin E, vitamin C, vitamin A, and tea polyphenols) and antioxidant enzymes (e.g., superoxide dismutase, catalase, glutathione reductase, and glutathione peroxidases) exert synergistic actions in scavenging free radicals. There has been growing evidence over the past three decades showing that malnutrition (e.g., dietary deficiencies of protein, selenium, and zinc) or excess of certain nutrients (e.g., iron and vitamin C) gives rise to the oxidation of biomolecules and cell injury. A large body of the literature supports the notion that dietary antioxidants are useful radioprotectors and play an important role in preventing many human diseases (e.g., cancer, atherosclerosis, stroke, rheumatoid arthritis, neurodegeneration, and diabetes). The knowledge of enzymatic and non-enzymatic oxidative defense mechanisms will serve as a guiding principle for establishing the most effective nutrition support to ensure the biological safety of manned space missions.

Cancer Res. 1994 Jul 1;54(13):3346-51.

The selective antiproliferative effects of alpha-tocopheryl hemisuccinate and cholesteryl hemisuccinate on murine leukemia cells result from the action of the intact compounds.

Fariss MW, Fortuna MB, Everett CK, Smith JD, Trent DF, Djuric Z.

In the present study we have established that the antitumor activity of alpha-tocopheryl succinate (TS, vitamin E succinate) and cholesteryl succinate (CS) result from the action of the intact TS and CS compounds and not from the release of alpha-tocopherol, cholesterol, or succinate. We report that treatment of murine leukemia cell lines C1498 (myeloid) and L1210 (lymphocytic), with the tris salts of TS or CS, but not alpha-tocopherol and tris succinate or cholesterol and tris succinate, significantly inhibit the growth of these tumor cells and significantly enhance doxorubicin-induced tumor cell kill in a similar fashion. In contrast, the treatments mentioned above did not adversely affect the growth of murine normal bone marrow cells (colony-forming unit-granulocyte-macrophage). In fact, colony-forming unit granulocyte-macrophage cell growth was stimulated by exposure to CS and TS (as well as their ether analogues) at concentrations above 100 microM. Furthermore, pretreatment of colony-forming unit granulocyte-macrophage cells with TS or CS appears to protect these normal cells from the lethal effect of doxorubicin exposure. Selective inhibition of leukemia cell proliferation (identical to that noted for CS and TS) was also observed following the treatment of cells with the nonhydrolyzable ether forms of CS (cholesteryloxybutyric acid) and TS (alpha-tocopheryloxybutyric acid). These findings suggest that TS, alpha-tocopheryloxybutyric acid, CS, and cholesteryloxybutyric acid may prove clinically useful as selective antitumor agents when administered alone or in combination with doxorubicin by a route that ensures tissue accumulation of the intact compound.

J Surg Res. 2000 Jan;88(1):23-5.

Peptide YY augments gross inhibition by vitamin E succinate of human pancreatic cancer cell growth.

Heisler T, Towfigh S, Simon N, Liu C, McFadden DW.

BACKGROUND: Vitamin E succinate (VES) significantly inhibits cell growth in vitro in breast, prostate, and skin cancer cell lines. Our study demonstrated similar inhibitory effects on Mia PaCa-2 pancreatic cancer cells at the same concentration of VES (10 pg/ml). Peptide YY (PYY) also inhibits pancreatic cancer cell growth in vitro. We observed a significant additive effect on growth inhibition in Mia PaCa cells treated with both VES and PYY. METHODS: Human pancreatic ductal adenocarcinoma Mia PaCa-2 cells were cultured and treated once with either 10 pg/ml of VES or 500 pmols of PYY or with both agents together. The control group received an equivalent volume of solvents. MTT assay was performed at 24, 48, and 72 h to evaluate cell viability. RESULTS: Pancreatic cancer cell growth was reduced in all groups treated with PYY and VES. Student's t test was used to analyze the data for each treatment group. At 72 h, both PYY and vitamin E significantly inhibited cell growth compared to control. Combining the agents resulted in a dramatic additive inhibition of growth. CONCLUSION: PYY and vitamin E both inhibit growth of pancreatic cancer cells in vitro with a significant increase in effect when used in combination.

Free Radic Biol Med. 2004 Jan 1;36(1):1-15.

New perspectives on vitamin E: gamma-tocopherol and carboxyelthylhydroxychroman metabolites in biology and medicine.

Hensley K, Benaksas EJ, Bolli R, Comp P, Grammas P, Hamdheydari L, Mou S, Pye QN, Stoddard MF, Wallis G, Williamson KS, West M, Wechter WJ, Floyd RA.

Vitamin E (alpha-tocopherol or alphaT) has long been recognized as a classic free radical scavenging antioxidant whose deficiency impairs mammalian fertility. In actuality, alpha-tocopherol is one member of a class of phytochemicals that are distinguished by varying methylation of a chroman head group. Early studies conducted between 1922 and 1950 indicated that alpha-tocopherol was specific among the tocopherols in allowing fertility of laboratory animals. The unique vitamin action of alphaT, combined with its prevalence in the human body and the similar efficiency of tocopherols as chain-breaking antioxidants, led biologists to almost completely discount the "minor" tocopherols as topics for basic and clinical research. Recent discoveries have forced a serious reconsideration of this conventional wisdom. New and unexpected biological activities have been reported for the desmethyl tocopherols, such as gamma-tocopherol, and for specific tocopherol metabolites, most notably the carboxyethyl-hydroxychroman (CEHC) products. The activities of these other tocopherols do not map directly to their chemical antioxidant behavior but rather reflect anti-inflammatory, antineoplastic, and natriuretic functions possibly mediated through specific binding interactions. Moreover, a nascent body of epidemiological data suggests that gamma-tocopherol is a better negative risk factor for certain types of cancer and myocardial infarction than is a alpha-tocopherol. The potential public health implications are immense, given the extreme popularity of alphaT supplementation which can unintentionally deplete the body of gamma-tocopherol. These findings may or may not signal a major paradigm shift in free radical biology and medicine. The data argue for thorough experimental and epidemiological reappraisal of desmethyl tocopherols, especially within the contexts of cardiovascular disease and cancer biology.

Am J Epidemiol. 2003 Feb 15;157(4):335-44.

Prospective study of antioxidant micronutrients in the blood and the risk of developing prostate cancer.

Huang HY, Alberg AJ, Norkus EP, Hoffman SC, Comstock GW, Helzlsouer KJ.

Antioxidant micronutrients may have chemopreventive effects. The authors examined the associations between prediagnostic blood levels of micronutrients and prostate cancer risk in two nested case-control studies of 9,804 and 10,456 male residents of Washington County, Maryland, who donated blood in 1974 (CLUE I) and 1989 (CLUE II), respectively. Until 1996, 182 men for whom adequate serum remained for assays in the CLUE I cohort and 142 men in the CLUE II cohort developed prostate cancer. Each case was matched with two controls by age, gender, race, and date of blood donation. In both cohorts, cases and controls had similar concentrations of alpha-carotene, beta-carotene, total carotene, beta-cryptoxanthin, lutein, lycopene, retinol, and ascorbic acid; serum alpha-tocopherol was weakly associated with prostate cancer risk. Higher retinyl palmitate concentrations were associated with a lower risk in CLUE I but not CLUE II. In CLUE I, cases had lower concentrations of gamma-tocopherol than did controls ($p = 0.02$), but no dose-response trend was observed. A strong inverse association between gamma-tocopherol and prostate cancer risk was observed in CLUE II. Findings do not replicate previous reports of a protective association between lycopene and prostate cancer, but they suggest potential chemopreventive effects of gamma-tocopherol on prostate cancer.

Biosci Biotechnol Biochem. 2003 Jul;67(7):1623-7.

Anti-angiogenic activity of tocotrienol.

Inokuchi H, Hirokane H, Tsuzuki T, Nakagawa K, Igarashi M, Miyazawa T.

The anti-angiogenic property of vitamin E compounds, with particular emphasis on tocotrienol, has been investigated in vitro. Tocotrienol, but not tocopherol, inhibited both the proliferation and tube formation of bovine aortic endothelial cells, with delta-tocotrienol appearing the highest activity. Also, delta-tocotrienol reduced the vascular endothelial growth factor-stimulated tube formation by human umbilical vein endothelial cells. Our findings suggest that tocotrienol has potential use as a therapeutic dietary supplement for minimizing tumor angiogenesis.

Nutr Cancer. 2000;36(1):90-100.

Vitamin E succinate induces apoptosis in human prostate cancer cells: role for Fas in vitamin E succinate-triggered apoptosis.

Israel K, Yu W, Sanders BG, Kline K.

The apoptosis-triggering properties of vitamin E succinate (VES, RRR-alpha-tocopheryl succinate) for human LNCaP and PC-3 prostate carcinoma cells and normal PrEC human prostate epithelial cells were investigated. LNCaP and PC-3 cells were sensitive to VES-induced apoptosis, with 100% and 60% of cells undergoing apoptosis after three days of treatment with 10 micrograms of VES/ml, respectively. PrEC cells were resistant to VES-induced apoptosis. Treatment of prostate cells with agonistic anti-Fas antibody triggered apoptosis in approximately 50% of PC-3 cells within 48 hours, whereas LNCaP and PrEC cells were resistant. Prostate cells simultaneously treated with VES and agonistic anti-Fas antibodies revealed 1) no effect on PrEC cells, 2) an additive effect on Fas-sensitive PC-3 cells, and 3) a synergistic effect on LNCaP cells. VES treatment of LNCaP cells caused depletion of cytosolic 43-kDa Fas, enhanced membrane levels of 43-kDa Fas, and induced Fas sensitivity. PC-3 cells expressed high levels of membrane 43-kDa Fas that were enhanced by VES treatments. Fas ligand expression by LNCaP cells was enhanced by VES treatments. In summary, VES triggers apoptosis in human prostate carcinoma cells but not normal prostate cells in vitro, and VES modulates Fas signaling.

Am J Clin Nutr. 2001 Dec;74(6):714-22.

gamma-tocopherol, the major form of vitamin E in the US diet, deserves more attention.

Jiang Q, Christen S, Shigenaga MK, Ames BN.

gamma-tocopherol is the major form of vitamin E in many plant seeds and in the US diet, but has drawn little attention compared with alpha-tocopherol, the predominant form of vitamin E in tissues and the primary form in supplements. However, recent studies indicate that gamma-tocopherol may be important to human health and that it possesses unique features that distinguish it from alpha-tocopherol. gamma-Tocopherol appears to be a more effective trap for lipophilic electrophiles than is alpha-tocopherol. gamma-Tocopherol is well absorbed and accumulates to a significant degree in some human tissues; it is metabolized, however, largely to 2,7,8-trimethyl-2-(beta-carboxyethyl)-6-hydroxychroman (gamma-CEHC), which is mainly excreted in the urine. gamma-CEHC, but not the corresponding metabolite derived from alpha-tocopherol, has natriuretic activity that may be of physiologic importance. Both gamma-tocopherol and gamma-CEHC, but not alpha-tocopherol, inhibit cyclooxygenase activity and, thus, possess antiinflammatory properties. Some human and animal studies indicate that plasma concentrations of gamma-tocopherol are inversely associated with the incidence of cardiovascular disease and prostate cancer. These distinguishing features of gamma-tocopherol and its metabolite suggest that gamma-tocopherol may contribute significantly to human health in ways not recognized previously. This possibility should be further evaluated, especially considering that high doses of alpha-tocopherol deplete plasma and tissue gamma-tocopherol, in contrast with supplementation with gamma-tocopherol, which increases both. We review current information on the bioavailability, metabolism, chemistry, and nonantioxidant activities of gamma-tocopherol and epidemiologic data concerning the relation between gamma-tocopherol and cardiovascular disease and cancer.

Surgery. 2002 Jan;131(1):85-91.

Vitamin E inhibits melanoma growth in mice.

Malafa MP, Fokum FD, Mowlavi A, Abusief M, King M.

BACKGROUND: Previous work has demonstrated that vitamin E succinate (VES), an ester analogue of vitamin E, inhibits the growth of melanoma in vitro. However, there is no information about the effect of VES on melanoma in vivo. We investigated the effect of VES on melanoma in vitro and in vivo. METHODS: The effect of VES on the proliferation and apoptosis of the B16F10 murine melanoma cell line was determined by a modified Cell Titer 96 AQ assay and a cell death detection enzyme-linked immunosorbent assay, respectively. The in vivo effect of VES on B16F10 melanoma cells allografted in athymic nude mice was investigated. The mechanism of the in vivo antitumor effect of VES was determined by immunohistochemical detection of proliferation and apoptosis. RESULTS: VES decreased cell proliferation (P =.0001) and increased cell apoptosis (P =.0001) in a dose-dependent manner in vitro. Also, VES significantly inhibited melanoma growth in mice (P =.0013). The VES antitumor effect in vivo was associated with a significant increase in the melanoma apoptosis rate (P =.0256). CONCLUSIONS: This is the first report of the antimelanoma effect of VES in vivo. The mechanism of the antimelanoma effect of VES in vivo involves the promotion of tumor cell apoptosis. These findings support future investigations of VES as a therapeutic micronutrient against melanoma.

J Surg Res. 2000 Sep;93(1):163-70.

Vitamin E succinate promotes breast cancer tumor dormancy.

Malafa MP, Neitzel LT.

BACKGROUND: Vitamin E succinate (VES) is the most potent antitumor analogue of vitamin E. Despite many reports of VES's antitumor activity in vitro, there is little information about its antitumor effects in vivo. MATERIALS AND METHODS: We investigated the effect of VES on the growth of human breast cancer cells in vitro and in vivo. RESULTS: VES decreased cell viability in MDA-MB-231 and MCF-7 human breast cancer cells. Although VES increased apoptosis in MDA-MB-231 cells, it had no effect on apoptosis in MCF-7 cells. The inhibitory effect of VES on cell growth was specific for the intact molecule because a markedly reduced effect was noted when either vitamin E or succinic acid was administered alone. VES inhibited the growth of MDA-MB-231 cells in nude mice. Also, VES was found to inhibit vascular endothelial growth factor (VEGF) gene expression in MDA-MB-231 cells. CONCLUSIONS: VES inhibits the growth of breast cancer cells in vitro and in vivo. This is the first report of VES inhibition of established tumor growth in vivo. The mechanism of VES's in vivo effects may involve inhibition of tumor angiogenesis since VES inhibits VEGF gene expression.

Ann N Y Acad Sci. 2004 Dec;1031:401-4.

Antiangiogenic potency of vitamin E.

Miyazawa T, Tsuzuki T, Nakagawa K, Igarashi M.

We investigated the antiangiogenic property and mechanism of vitamin E compounds, with particular emphasis on tocotrienol (T3), a natural analogue of tocopherol (Toc). T3 inhibited both the proliferation and tube formation of bovine aortic endothelial cells, with delta-T3 appearing to have the highest activity. delta-T3 also reduced the vascular endothelial growth factor (VEGF)-stimulated tube formation by human umbilical vein endothelial cells. Moreover, delta-T3 inhibited the new blood vessel formation on the growing chick embryo chorioallantoic membrane (assay for in vivo angiogenesis). Orally administered T3 suppressed the tumor cell-induced angiogenesis in the mouse dorsal air sac assay. In contrast with T3, Toc showed very weak inhibition. Based on DNA microarray analysis, antiangiogenic effect of T3 was attributable in part to regulation of intracellular VEGF signaling (phospholipase C-gamma and protein kinase C). Our findings suggest that T3 has potential as a therapeutic dietary supplement for preventing angiogenic disorders.

Br J Cancer. 2001 Jan 5;84(1):87-9.

Selective cancer cell killing by alpha-tocopheryl succinate.

Neuzil J, Weber T, Gellert N, Weber C.

We report that alpha-tocopheryl succinate, a vitamin E analogue with pro-apoptotic properties, selectively kills cells with a malignant or transformed phenotype, i.e. multiple haematopoietic and carcinoma cell lines, while being non-toxic to normal, i.e. primary and non-transformed cells. These findings strongly suggest a potential of this micronutrient in the therapy and/or prevention of cancer without significant side-effects.

Apoptosis. 2002 Apr;7(2):179-87.

Vitamin E analogs: a new class of multiple action agents with anti-neoplastic and anti-atherogenic activity.

Neuzil J, Kagedal K, Andera L, Weber C, Brunk UT.

The incidence of cancer and atherosclerosis, two most common causes of death in developed countries, has been stagnating or, even, increasing. Drugs effective against such conditions are needed and, in this regard, the potential anti-atherosclerotic activity of vitamin E analogs has been studied extensively. Surprisingly, recent results indicate that these agents may also exert anti-neoplastic effects. Here we review the evidence that particular analogs of vitamin E may act as both antiatherogenic and anti-cancer agents, and discuss the possible molecular bases for these actions.

Nutr Cancer. 1994;22(3):233-45.

Modification of the effect of tamoxifen, cis-platin, DTIC, and interferon-alpha 2b on human melanoma cells in culture by a mixture of vitamins.

Prasad KN, Hernandez C, Edwards-Prasad J, Nelson J, Borus T, Robinson WA.

The effect of a mixture of vitamins in modifying the efficacy of commonly used drugs in the treatment of human melanoma has not been studied. Vitamin C and d-alpha-tocopheryl succinate (alpha-TS) alone reduced the growth of human melanoma (SK-30) cells in culture, whereas beta-carotene (BC), 13-cis-retinoic acid (RA), or sodium selenite alone was ineffective. RA caused morphological changes, as evidenced by flattening of cells and formation of short cytoplasmic processes. A mixture of four vitamins (vitamin C, BC, alpha-TS, and RA) was more effective in reducing growth of human melanoma cells than a mixture of three vitamins. The growth-inhibitory effect of cis-platin, decarbazine, tamoxifen, and recombinant interferon-alpha 2b was enhanced by vitamin C alone, a mixture of three vitamins (BC, alpha-TS, and RA), and a mixture of four vitamins (vitamin C, BC, alpha-TS, and RA) that contained 50 micrograms/ml of vitamin C. These data show that a mixture of three or four vitamins can enhance the growth-inhibitory effect of currently used chemotherapeutic agents on human melanoma cells.

Nutr Cancer. 1996;26(1):11-9.

Effect of individual and multiple antioxidant vitamins on growth and morphology of human nontumorigenic and tumorigenic parotid acinar cells in culture.

Prasad KN, Kumar R.

The effects of individual and multiple antioxidant vitamins on growth and morphology of human nontumorigenic (2HPC8) and tumorigenic (2HP1G) parotid acinar cells in culture have not been investigated. Our study showed that tumorigenic acinar cells were more sensitive than nontumorigenic acinar cells to individual vitamins such as vitamin C, beta-carotene (BC), d-alpha-tocopheryl succinate (alpha-TS), and retinoic acid (RA) and a mixture of four vitamins (vitamin C, BC, alpha-TS, and RA). The effect of individual vitamins on tumorigenic acinar cells depended on the dose and the type of vitamins. Vitamin C at a low concentration stimulated growth, but at a high concentration it inhibited growth. BC was most effective in reducing growth, and it alone caused extensive morphological changes in tumorigenic acinar cells. A mixture of four vitamins at appropriate doses was more effective than a mixture of two or three vitamins at the same doses in reducing the growth of tumorigenic acinar cells. The extent of growth inhibition depended on the dose and the type of vitamins. Our results suggest that the use of multiple antioxidant vitamins is essential for a maximal reduction in cancer incidence among a high-risk population. The use of one or two vitamins may be ineffective or even harmful.

J Am Coll Nutr. 2003 Apr;22(2):108-17.

Alpha-tocopheryl succinate, the most effective form of vitamin E for adjuvant cancer treatment: a review.

Prasad KN, Kumar B, Yan XD, Hanson AJ, Cole WC.

In 1982, it was established that alpha-tocopheryl succinate (alpha-TS) was the most effective form of vitamin E in comparison to alpha-tocopherol, alpha-tocopheryl acetate and alpha-tocopheryl nicotinate in inducing differentiation, inhibition of proliferation and apoptosis in cancer cells, depending upon its concentration. During the last two decades, several studies have confirmed this observation in rodent and human cancer cells in culture and in vivo (animal model). The most exciting aspect of this alpha-TS effect is that it does not affect the proliferation of most normal cells. In spite of several studies published on the anti-cancer properties of alpha-TS, the value of this form of vitamin E has not drawn significant attention from researchers and clinicians. Therefore, a critical review on the potential role of alpha-TS in the management of cancer is needed. In addition, such a review can also provide in-depth analysis of existing literature on this subject. alpha-TS treatment causes extensive alterations in gene expression; however, only some can be attributed to differentiation, inhibition of proliferation and apoptosis. alpha-TS also enhances the growth-inhibitory effect of ionizing radiation, hyperthermia, some chemotherapeutic agents and biological response modifiers on tumor cells, while protecting normal cells against some of their adverse effects. Thus, alpha-TS alone or in combination with dietary micronutrients can be useful as an adjunct to standard cancer therapy by increasing tumor response and possibly decreasing some of the toxicities to normal cells.

Biochim Biophys Acta. 2000 May 31;1485(2-3):129-44.

Lipoprotein-associated alpha-tocopheryl-succinate inhibits cell growth and induces apoptosis in human MCF-7 and HBL-100 breast cancer cells.

Pussinen PJ, Lindner H, Glatter O, Reicher H, Kostner GM, Wintersperger A, Malle E, Sattler W.

alpha-Tocopheryl succinate (alpha-TS) is a potent inhibitor of tumor cell proliferation. The goal of the present study was to investigate whether and to what extent alpha-TS associates with plasma lipoproteins and if alpha-TS-enriched lipoproteins inhibit breast cancer cell growth in a manner comparable to the free drug. In vitro enrichment of human plasma revealed that alpha-TS readily associated with the main lipoprotein classes, findings confirmed in vivo in mice. At the highest alpha-TS concentrations, lipoproteins carrying 50000 (VLDL), 5000 (LDL) and 700 (HDL) alpha-TS molecules per lipoprotein particle were generated. alpha-TS enrichment generated lipoprotein particles with slightly decreased density and increased particle radius. To study whether the level of LDL-receptor (LDL-R) expression affects alpha-TS uptake from apoB/E containing lipoprotein particles human breast cancer cells with low (MCF-7) and normal (HBL-100) LDL-R expression were used. The uptake of free, VLDL- and (apoE-free) HDL(3)-associated alpha-TS was nearly identical for both cell lines. In contrast, uptake of LDL-associated alpha-TS by HBL-100 cells (normal LDL-R expression) was about twice as high as compared to MCF-7 cells (low LDL-R expression). VLDL and LDL-associated alpha-TS inhibited proliferation most effectively at the highest concentration of alpha-TS used (100% inhibition of MCF-7 growth with 20 microg/ml of lipoprotein-associated alpha-TS). However, also alpha-TS-free VLDL and LDL inhibited HBL-100 cell proliferation up to 55%. In both cell lines, alpha-TS-enriched HDL(3) inhibited cell growth by 40-60%. Incubation of both cell lines in the presence of free or lipoprotein-associated alpha-TS resulted in DNA fragmentation indicative of apoptosis. Collectively, the present findings demonstrate that: (1) alpha-TS readily associates with lipoproteins in vitro and in vivo; (2) the lipoprotein-enrichment efficacy was dependent on the particle size and/or the triglyceride content of the lipoprotein; (3) uptake of LDL-associated alpha-TS was apparently dependent on the level of LDL-R expression; and (4) lipoproteins were efficient alpha-TS carriers inducing reduced cell proliferation rates and apoptosis in human breast cancer cells as observed for the free drug.

FASEB J. 2001 Nov;15(13):2314-25.

Vitamin E: protective role of a Janus molecule.

Ricciarelli R, Zingg JM, Azzi A.

Since the discovery of vitamin E in 1922, its deficiency has been associated with various disorders, particularly atherosclerosis, ischemic heart disease, and the development of different types of cancer. A neurological syndrome associated with vitamin E deficiency resembling Friedreich ataxia has also been described. Whereas epidemiological studies have indicated the role of vitamin E in preventing the progression of atherosclerosis and cancer, intervention trials have produced contradictory results, indicating strong protection in some cases and no significant effect in others. Although it is commonly believed that phenolic compounds like vitamin E exert only a protective role against free radical damage, antioxidant molecules can exert other biological functions. For instance, the antioxidant activity of 17-beta-estradiol is not related to its role in determining secondary sexual characters, and the antioxidant capacity of all-trans-retinal is distinguished from its role in rhodopsin and vision. Thus, it is not unusual that alpha-tocopherol (the most active form of vitamin E) has properties independent of its antioxidant/radical scavenging ability. The Roman god Janus, shown in ancient coins as having two faces in one body, inspired the designation of 'Janus molecules' for these substances. The new biochemical face of vitamin E was first described in 1991, with an inhibitory effect on cell proliferation and protein kinase C activity. After a decade, this nonantioxidant role of vitamin E is well established, as confirmed by authoritative studies of signal transduction and gene regulation. More recently, a tocopherol binding protein with possible receptor function has been discovered. Despite such important developments in understanding the molecular mechanism and the targets of vitamin E, its new Janus face is not fully elucidated. Greater knowledge of the molecular events related to vitamin E will help in selecting the parameters for clinical intervention studies such as population type, dose response effects, and possible synergism with other compounds.

J Urol. 1986 Aug;136(2):529-31.

Vitamin E enhances the chemotherapeutic effects of adriamycin on human prostatic carcinoma cells in vitro.

Ripoll EA, Rama BN, Webber MM.

Vitamin E (tocopherol) enhances the growth inhibitory effects of adriamycin (ADR) on a variety of cancer cells in vitro. The role of vitamin E (d-alpha-tocopheryl) acid succinate in adjuvant chemotherapy with ADR was assessed in DU-145 human prostatic carcinoma cells in culture. Adriamycin produced a dose-dependent growth inhibition of DU-145 cells. The ID50 of DU-145 cells on the criteria: of clonal assay was 13 ng./ml. and of cell count assay was 14 ng./ml. Vitamin E succinate also inhibited the growth of DU-145 human prostatic carcinoma cells in a dose-dependent manner. 4.4 micrograms./ml. and 5.4 micrograms./ml. vitamin E succinate in the culture medium produced inhibition of growth to 50 per cent of control (ID50) in the clonal and the cell count assays respectively. When adriamycin and vitamin E succinate were used in combination, both additive and synergistic effects were observed, depending on the concentration of vitamin E succinate used. Doses of vitamin E succinate greater than its ID50 had a synergistic effect while doses smaller than its ID50 had an additive effect. In either case, the presence of vitamin E succinate caused an enhancement of tumor cell cytotoxicity of adriamycin while decreasing its ID50. Equivalent concentrations of sodium succinate and ethanol used to dissolve vitamin E succinate did not have any effect on DU-145 cells. Thus, it is concluded that the effect of vitamin E succinate is due to vitamin E and not due to succinate or ethanol. These results suggest that vitamin E may have a role in the treatment of human prostatic cancer as an adjuvant agent to adriamycin.

J Surg Res. 2001 Jan;95(1):19-22.

Alpha-tocopherol succinate inhibits growth of gastric cancer cells in vitro.

Rose AT, McFadden DW.

BACKGROUND: Vitamin E in the form of alpha-tocopherol succinate (ATS) has been shown to inhibit growth of several cancer cell lines in vitro, including pancreas, breast, and prostate. No data exist on the effect of ATS on gastric cancer cell viability. METHODS: A gastric cancer cell line in suspension form, KATO-III, was plated in 96-well plates at 30,000 cells per well with 100 microl RPMI media. The cells were allowed to incubate for 24 h and were then treated with ATS at doses of 25, 50, or 100 microg/ml. The ATS was dissolved in 1% EtOH solution and control cells received an identical solution of EtOH without ATS. Treated cells were incubated for 24, 48, or 72 h. At the completion of the treatment period, MTT assay was performed to determine cell viability. Statistical analysis was performed using Student's t test. RESULTS: All doses of ATS resulted in inhibition of growth of the KATO-III cells. Both 100 and 50 microg/cc doses inhibited growth at all time points ($P<0.005$), with 48- and 72-h treatments more effective than 24-h treatment. At 24 and 48 h, 100 microg/cc was more effective at inhibition of growth than 50 microg/ml ($P<0.005$), but by 72 h the effects of the doses were equivalent; 25 microg/ml inhibited cell growth only at 48 and 72 h. At all time points, 50 and 100 microg/ml doses were more effective at inhibiting cell growth than 25 microg/ml. Conclusions. ATS inhibits gastric carcinoma cell growth in vitro in a dose- and time-dependent fashion. In vivo studies are indicated to further evaluate the potential benefit of this antioxidant against gastric cancer.

Braz J Med Biol Res. 2000 Aug;33(8):929-36.

alpha-Tocopherol enhances tumour growth inhibition by cis-dichlorodiammine platinum (II).

Sarna S, Kumar A, Bhola RK.

Present studies indicate that alpha-tocopherol enhances the efficacy of cisplatin as demonstrated by inoculation of Dalton's lymphoma cells incubated with either cisplatin (5 or 10 microg/ml) alone or cisplatin + alpha-tocopherol (25 or 50 microg/ml) into C3H/He mice. Tumour cells (3 x 10(6) cells/mouse) incubated with cisplatin grow slowly in syngeneic mice as indicated by the late appearance of tumour. However, mice failed to develop tumour when inoculated with tumour cells incubated with cisplatin + alpha-tocopherol. When the animals were challenged with tumour cells (3 x 10(6) cells/mouse) on the 15th day after the initial inoculation, 30-50% survived more than 60 days, with 10% tumour-free survivors being observed in some groups. Antitumour activity was higher in mice receiving lymphoma cells (3 x 10(6) cells/mouse) preincubated with cisplatin + alpha-tocopherol compared to cisplatin alone. Tumour-bearing mice receiving cisplatin in combination with different concentrations of alpha-tocopherol exhibited significantly higher ($P<0.001$) intratumour platinum content (123-306%) but without any change in the kidney platinum content as compared to those receiving cisplatin (5 or 10 microg/ml) alone. Enhancement of cisplatin-induced tumour growth inhibition is probably due to the modulation of tumour cell membrane permeability by alpha-tocopherol. alpha-Tocopherol might increase the influx of cisplatin into tumour cells, causing the DNA repair machinery to be less efficient due to increased efficiency of adduct formation in the DNA molecule. This effect of alpha-tocopherol can render cisplatin more effective as an antitumour agent.

Eur J Cancer B Oral Oncol. 1996 Mar;32B(2):114-9.

Vitamin E inhibits experimental carcinogenesis and tumour angiogenesis.

Shklar G, Schwartz JL.

In an experiment in which vitamin E inhibited carcinogenesis, it was found that tumour angiogenesis and tumour growth-factor alpha (TGF alpha) expression were also inhibited. Forty male golden hamsters were divided into four equal groups. Group 1 animals had the left buccal pouches painted three times weekly with 7,12-dimethylbenz(a)anthracene (DMBA) for 14 weeks. Group 2 animals had the same procedure of DMBA applications but also received alpha tocopherol. Groups 3 and 4 were vitamin E and untreated controls. Angiogenesis was studied with factor 8-related antigen (F8-RA) which identifies endothelial cells. TGF alpha was studied with the appropriate antibody. Staining was effected by the standard avidin-biotin horseradish peroxidase system. Mean tumour volume was significantly lower in the DMBA-vitamin E group compared to the tumour control group. Angiogenesis was significantly inhibited in the DMBA-vitamin E group and TGF alpha expression was also inhibited. It is suggested that inhibition of tumour angiogenesis by vitamin E may be an additional mechanism for the anticancer action of vitamin E.

Nutr Cancer. 2001;41(1-2):119-25.

Green tea catechins and vitamin E inhibit angiogenesis of human microvascular endothelial cells through suppression of IL-8 production.

Tang FY, Meydani M.

Epidemiological and animal studies have indicated that consumption of green tea and high vitamin E intake are associated with a reduced risk of developing certain forms of cancer. However, the inhibitory mechanism of green tea catechins and vitamin E in angiogenesis, an important process in tumor growth, has not been well established. In the present study, alpha-tocopherol and several major catechins of green tea (catechin, epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate) were tested for their ability to inhibit tube formation in vitro using a model in which human microvascular endothelial cells were exposed to a constant rate of a physiologically low level of H2O2. In this model, the production of interleukin (IL)-8 by human microvascular endothelial cells at a low level of H2O2 was required for angiogenesis, as assessed by tube formation in three-dimensional gel in culture. Vitamin E (d-alpha-tocopherol, 40 microM) in the culture media significantly reduced IL-8 production and angiogenesis. Among the green tea catechins, epigallocatechin (0.5-1 microM) was the most effective in reducing IL-8 production and inhibiting angiogenesis. These results suggest that consumption of green tea catechins or supplemental intake of vitamin E may have preventive effects on tumor development, mediated, at least in part, through inhibition of angiogenesis via suppression of IL-8 production.

Cell Growth Differ. 1995 Jun;6(6):655-63.

Growth inhibition and apoptosis of RL human B lymphoma cells by vitamin E succinate and retinoic acid: role for transforming growth factor beta.

Turley JM, Funakoshi S, Ruscetti FW, Kasper J, Murphy WJ, Longo DL, Birchenall-Roberts MC.

Vitamin E succinate (VES) and all-trans-retinoic acid (RA) were determined to be growth inhibitory for B lymphoma cells in vitro. RL, an Epstein-Barr virus-negative human cell line, was growth suppressed 87% with VES (5 micrograms/ml) and 58% with RA (10(-6) M); both agents blocked the cells in G1 of the cell cycle. The antiproliferative effect of VES seems to be independent of its potential antioxidant property because both fat- and water-soluble antioxidants were found to have no effect on RL cell proliferation. VES and RA increased IgM antibody concentrations in cell supernatants 5.8- and 9.9-fold, respectively. DNA fragmentation and flow cytometry studies showed VES- and RA-induced apoptosis in RL cells. VES- and RA-treated RL cells gradually underwent apoptosis over time with maximal induction occurring at days 6 and 5 of culture, respectively. A role for transforming growth factor beta in VES- and RA-mediated RL growth suppression is indicated by increased ligand and type II receptor protein expression. Furthermore, neutralizing antibodies to transforming growth factor beta 1 partially blocked the growth suppressive action of both VES and RA, thus suggesting that a TGF-beta autocrine negative loop was involved in VES and RA suppression of RL cell growth.

World J Gastroenterol. 2002 Feb;8(1):26-30.

RRR-alpha-tocopheryl succinate inhibits human gastric cancer SGC-7901 cell growth by inducing apoptosis and DNA synthesis arrest.

Wu K, Zhao Y, Liu BH, Li Y, Liu F, Guo J, Yu WP.

AIM: To investigate the effects of growth inhibition of human gastric cancer SGC-7901 cell with RRR-alpha-tocopheryl succinate (VES), a derivative of natural Vitamin E, via inducing apoptosis and DNA synthesis arrest. METHODS: Human gastric cancer SGC-7901 cells were regularly incubated in the presence of VES at 5, 10 and 20mg x L(-1) (VES was dissolved in absolute ethanol and diluted in RPMI 1640 complete condition media correspondingly to a final concentration of VES and 1 mL x L(-1) ethanol), succinic acid and ethanol equivalents as vehicle (VEH) control and condition media only as untreated (UT) control. Trypan blue dye exclusion analysis and MTT assay were applied to detect the cell proliferation. Cells were pulsed with 37kBq of tritiated thymidine and (3H) TdR uptake was measured to observe DNA synthesis. Apoptotic morphology was observed by electron microscopy and DAPI staining. Flow cytometry and terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) assay were performed to detect VES-triggered apoptosis.RESULTS: VES inhibited SGC-7901 cell growth in a dose-dependent manner. The growth curve showed suppression by 24.7%, 49.2% and 68.7% following 24h of VES treatment at 5, 10 and 20 mg x L(-1), respectively, similar to the findings from MTT assay. DNA synthesis was evidently reduced by 35%, 45% and 98% after 24h VES treatment at 20mg x L(-1) and 48 h at 10 and 20mg x L(-1), respectively. VES induced SGC-7901 cells to undergo apoptosis with typically apoptotic characteristics, including morphological changes of chromatin condensation, chromatin crescent formation/margination, nucleus fragmentation and apoptotic body formation, typical apoptotic sub-G1 peak by flow cytometry and increase of apoptotic cells by TUNEL assay in which 90% of cells underwent apoptosis after 48 h of VES treatment at 20 mg x L(-1). CONCLUSION: VES can inhibit human gastric cancer SGC-7901 cell growth by inducing apoptosis and DNA synthesis arrest. Inhibition of SGC-7901 cell growth by VES is dose- and time-dependent. Therefore VES can function as a potent chemotherapeutic agent against human gastric carcinogenesis.

Free Radic Res. 2000 Oct;33(4):407-18.

Mechanism of alpha-tocopheryl succinate-induced apoptosis of promyelocytic leukemia cells.

Yamamoto S, Tamai H, Ishisaka R, Kanno T, Arita K, Kobuchi H, Utsumi K.

Selective induction of apoptosis in tumor cells is important for treating patients with cancer. Because oxidative stress plays an important role in the process of apoptosis, we studied the effect of alpha-tocopheryl succinate (VES) on the fate of cultured human promyelocytic leukemia cells (HL-60). The presence of fairly low concentrations of VES inhibited the growth and DNA synthesis of HL-60 cells, and also induced their apoptosis via a mechanism that was inhibited by z-VAD-fluoromethylketone (z-VAD-fmk), an inhibitor of pan-caspases. VES activated various types of caspases, including caspase-3, 6, 8, and 9, but not caspase-1. VES triggered the reaction leading to the cleavage of Bid, a member of the death agonist Bcl-2 family, and released cytochrome c (Cyt.c) from the mitochondria into the cytosol by a z-VAD-fmk-inhibitable mechanism. VES transiently increased the intracellular calcium level [Ca2+]i and stimulated the release of Cyt.c in the presence of inorganic phosphate (Pi). However, high concentrations of VES (approximately 100 microM) hardly induced swelling of isolated mitochondria but depolarized the mitochondrial membrane potential by a cyclosporin A (CsA)-insensitive mechanism. These results indicate that VES-induced apoptosis of HL-60 cells might be caused by activation of the caspase cascade coupled with modulation of mitochondrial membrane function.

J Surg Res. 2002 Jun 1;105(1):65-8.

Vitamin E and the Y4 agonist BA-129 decrease prostate cancer growth and production of vascular endothelial growth factor.

Yu A, Somasundar P, Balsubramaniam A, Rose AT, Vona-Davis L, McFadden DW.

BACKGROUND: A biologically active form of vitamin E, alpha-tocopherol succinate (ATS), has been shown to induce apoptosis of hormone-refractory prostate cancer in vitro and inhibit cell growth in vivo. The gastrointestinal hormone peptide YY (PYY) has growth inhibitory activity against multiple cancer cell lines and is synergistic with ATS against breast and pancreatic cancer growth. BA-129, a specific Y4 receptor agonist, has growth inhibitory effects on pancreatic cancer in vitro. We investigated the effects of BA-129 and ATS on prostate cancer growth and evaluated their effects on vascular endothelial growth factor (VEGF) production. METHODS: A hormone-refractory human prostate cancer cell line, PC-3, was treated with ATS alone at 10 pg/ml, PYY or BA-129 alone at doses of 75 and 500 pmol/ml, or a combination of the two agents. Cell growth was measured by MTT assay and hemocytometry using trypan blue. Quantitative measurement of VEGF was performed by ELISA. Statistical analysis was achieved by ANOVA. RESULTS: ATS exhibited significant ($P < 0.05$) growth inhibitory effects in prostate cancer cells. PYY also inhibited growth ($P < 0.05$). ATS treatment reduced VEGF production ($P < 0.05$). PYY treatment increased VEGF. When ATS was given in combination with BA-129, VEGF production was further reduced ($P < 0.05$). CONCLUSIONS: Both PYY and ATS inhibit growth in hormone-refractory prostate cancer, with augmentation when used in combination. VEGF production is inhibited by vitamin E, but increased by PYY. ATS abolishes the augmented VEGF response to PYY. Our data suggest that PYY is involved in the regulation of VEGF production and prostate cancer growth.

Cancer Res. 1999 Feb 15;59(4):953-61.

Vitamin E succinate (VES) induces Fas sensitivity in human breast cancer cells: role for Mr 43,000 Fas in VES-triggered apoptosis.

Yu W, Israel K, Liao QY, Aldaz CM, Sanders BG, Kline K.

Fas (CD95/APO-1) is an important mediator of apoptosis. We show that Fas-resistant MCF-7, MDA-MB-231, and MDA-MB-435 human breast cancer cells become responsive to anti-Fas (CD95) agonistic antibody-triggered apoptosis after pretreatment or cotreatment with vitamin E succinate (VES; RRR-alpha-tocopheryl succinate). In contrast, no enhancement of anti-Fas agonistic antibody-triggered apoptosis was observed following VES pretreatment or cotreatment with Fas-sensitive primary cultures of human mammary epithelial cells, immortalized MCF-10A cells, or T47D human breast cancer cells. Although VES is itself a potent apoptotic triggering agent, the 6-h pretreatment procedure for Fas sensitization did not initiate VES-mediated apoptosis. The combination of VES plus anti-Fas in pretreatment protocols was synergistic, inducing 2.8-, 3.0-, and 6.3-fold enhanced apoptosis in Fas-resistant MCF-7, MDA-MB-231, and MDA-MB-435 cells, respectively. Likewise, cotreatment of Fas-resistant MCF-7, MDA-MB-231, and MDA-MB-435 cells with VES plus anti-Fas enhanced apoptosis 1.9-, 2.0-, and 2.6-fold, respectively. Functional knockout of Fas-mediated signaling with either Fas-neutralizing antibody (MCF-7-, MDA-MB-231-, and MDA-MB-435-treated cells) or Fas antisense oligomers (MDA-MB-435-treated cells only), reduced VES-triggered apoptosis by approximately 50%. Analyses of whole cell extracts from Fas-sensitive cells revealed high constitutive expression of Mr 43,000 Fas, whereas Fas-resistant cells expressed low levels that were confined to the cytosolic fraction. VES treatment of the Fas-resistant cells caused a depletion of cytosolic Mr 43,000 Fas with a concomitant increase in Mr 43,000 membrane Fas. These data show that VES can convert Fas-resistant human breast cancer cells to a Fas-sensitive phenotype, perhaps by translocation of cytosolic Mr 43,000 Fas to the membrane and show that VES-mediated apoptosis involves Mr 43,000 Fas signaling.

Cancer Res. 2001 Sep 1;61(17):6569-76.

Activation of extracellular signal-regulated kinase and c-Jun-NH(2)-terminal kinase but not p38 mitogen-activated protein kinases is required for RRR-alpha-tocopheryl succinate-induced apoptosis of human breast cancer cells.

Yu W, Liao QY, Hantash FM, Sanders BG, Kline K.

RRR-alpha-tocopherol succinate (vitamin E succinate, VES) is a potent, selective apoptotic agent for cancer cells but not normal cells. VES has been shown to inhibit the growth of a wide variety of tumor cells in cell culture and animal models. Studies addressing mechanisms of action of VES-induced apoptosis have identified transforming growth factor-beta, Fas/CD95-APO-1, and mitogen-activated protein kinase (MAPK) signaling pathway involvement. Here we show that MAPKs, the extracellular signal-regulated kinases (ERK), and the stress-activated protein kinases, c-Jun NH2-terminal kinases (JNK), but not p38, are critical mediators in VES-induced apoptosis of human breast cancer MDA-MB-435 cells. VES activates ERK1/2 and JNK both in level and duration of kinase activity. Expression of dominant negative mutants of ERK1, MAPK/ERK activator-1, or JNK1 but not p38 blocked phosphorylation of the substrate glutathione S-transferase-c-Jun and inhibited VES-induced apoptosis. Increased phosphorylation and transactivation activity of nuclear transcription factors c-Jun, ATF-2, and Elk-1 are observed after VES treatments; however, only c-Jun and ATF-2 appear to be involved in VES-induced apoptosis based on antisense blockage experiments. Collectively, these results imply a critical role for ERK1 and JNK1 but not p38 in VES-induced apoptosis of human MDA-MB-435 breast cancer cells.

Nutr Cancer. 1997;27(1):92-101.

RRR-alpha-tocopheryl succinate inhibits EL4 thymic lymphoma cell growth by inducing apoptosis and DNA synthesis arrest.

Yu W, Sanders BG, Kline K.

RRR-alpha-tocopheryl succinate (vitamin E succinate, VES) treatment of murine EL4 T lymphoma cells induced the cells to undergo apoptosis. After 48 hours of VES treatment at 20 micrograms/ml, 95% of cells were apoptotic. Evidence for the induction of apoptosis by VES treatments is based on staining of DNA for detection of chromatin condensation/fragmentation, two-color flow-cytometric analyses of DNA content, and end-labeled DNA and electrophoretic analyses for detection of DNA ladder formation. VES-treated EL4 cells were blocked in the G1 cell cycle phase; however, apoptotic cells came from all cell cycle phases. Analyses of mRNA expression of genes involved in apoptosis revealed decreased c-myc and increased bcl-2, c-fos, and c-jun mRNAs within three to six hours after treatment. Western analyses showed increased c-Jun, c-Fos, and Bcl-2 protein levels. Electrophoretic mobility shift assays showed increased AP-1 binding at 6, 12, and 24 hours after treatment and decreased c-Myc binding after 12 and 24 hours of VES treatment. Treatments of EL4 cells with VES+RRR-alpha-tocopherol reduced apoptosis without effecting DNA synthesis arrest. Treatments of EL4 cells with VES+rac-6-hydroxyl-2, 5,7,8-tetramethyl-chroman-2-carboxylic acid, butylated hydroxytoluene, or butylated hydroxyanisole had no effect on apoptosis or DNA synthesis arrest caused by VES treatments. Analyses of bcl-2, c-myc, c-jun, and c-fos mRNA levels in cells receiving VES + RRR-alpha-tocopherol treatments showed no change from cells receiving VES treatments alone, implying that these changes are correlated with VES treatments but are not causal for apoptosis. However, treatments with VES + RRR-alpha-tocopherol decreased AP-1 binding to consensus DNA oligomer, suggesting AP-1 involvement in apoptosis induced by VES treatments.

Proc Natl Acad Sci U S A. 2002 May 28;99(11):7408-13.

Vitamin E succinate inhibits the function of androgen receptor and the expression of prostate-specific antigen in prostate cancer cells.

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Although epidemiological evidence indicates that a daily supplement of vitamin E may reduce the risk of prostate cancer, the detailed mechanism underlying this effect remains unclear. Here we demonstrate that alpha-tocopheryl succinate (VES) can suppress the expression of prostate-specific antigen (PSA), a marker for the progression of prostate cancer. VES can also suppress androgen receptor (AR) expression by means of transcriptional and posttranscriptional modulation, but not ligand binding, nuclear translocation, or AR dimerization. This VES-mediated inhibition of AR is selective because VES does not repress the expression of other nuclear receptors. Cell growth studies further show that VES inhibits the growth of prostate cancer LNCaP cells. In contrast, hydroxyflutamide (HF), an antiandrogen currently used to treat prostate cancer patients, only slightly inhibits LNCaP cell growth. Interestingly, simultaneous addition of HF and VES results in a more significant inhibition of LNCaP cell growth. Moreover, selenomethionine (SM), a prostate cancer treatment adjuvant, shows an inhibitory effect on LNCaP cell growth, yet has no effect on the AR/PSA pathway. Together, our data indicate that VES may suppress androgen/AR-mediated cell growth and PSA expression by inhibiting AR expression at both the transcription and translation levels. This previously undescribed mechanism may explain how VES inhibits the growth of prostate cancer cells and help us to establish new therapeutic concepts for the prevention and treatment of prostate cancer.