

Leukemia and Lymphoma (Hodgkin's and Non-Hodgkin's Disease)

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ABSTRACTS

Angiogenesis in acute and chronic leukemias and myelodysplastic syndromes.

Aguayo A, Kantarjian H, Manshouri T, et al.

Blood. 2000 Sep 15; 96(6):2240-5.

Angiogenesis has been associated with the growth, dissemination, and metastasis of solid tumors. The aims of this study were to evaluate the vascularity and the levels of angiogenic factors in patients with acute and chronic leukemias and myelodysplastic syndromes (MDS). The numbers of blood vessels were measured in 145 bone marrow biopsies and the levels of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), tumor necrosis growth factor-alpha (TNF-alpha), tumor growth factor-alpha (TGF-alpha), and hepatocyte growth factor (HGF) were determined in 417 plasma samples. Except for chronic lymphocytic leukemia (CLL), vascularity was significantly higher in all leukemias and MDS compared with control bone marrows. The highest number of blood vessels and largest vascular area were found in chronic myeloid leukemia (CML). VEGF, bFGF, and HGF plasma levels were significantly increased in acute myeloid leukemia (AML), CML, CLL, chronic myelomonocytic leukemia (CMML), and MDS. HGF, TNF-alpha, and bFGF but not VEGF were significantly increased in acute lymphoblastic leukemia (ALL). TNF-alpha levels were significantly increased in all diseases except for AML and MDS. No significant increase was found in TGF-alpha in any leukemia or MDS. The highest plasma levels of VEGF were in CML, and the highest plasma levels of bFGF were in CLL. The levels of HGF were highest in CMML. These data suggest that vascularity and angiogenic factors are increased in leukemias and MDS and may play a role in the leukemogenic process

Modulation of immune dysfunction during murine leukaemia retrovirus infection of old mice by dehydroepiandrosterone sulphate (DHEAS).

Araghi-Niknam M, Liang B, Zhang Z, et al.

Immunology. 1997 Mar; 90(3):344-9.

Ageing, leukaemia and acquired immune deficiency syndrome (AIDS) are conditions with dysregulated cytokine production. As dehydroepiandrosterone sulphate (DHEAS) restored normal cytokine production in old mice its effects on retrovirally infected old mice were investigated. Retrovirus infection and ageing-induced immune dysfunction. Murine retrovirus-infected old C57BL/6 female mice consumed 0.22 or 0.44 microgram of DHEAS/mouse/day beginning 2 weeks postinfection for 10 weeks. DHEAS largely prevented the retrovirus-induced reduction in T-cell and B-cell mitogenesis. DHEAS supplement prevented loss of cytokines [interleukin-2 (IL-2) and interferon-gamma] secretion by mitogen-stimulated splenocytes representing T helper 1 (Th1) cell phenotypes. It also suppressed the retrovirus-induced, excessive production of cytokines (IL-6 and IL-10) by Th2 cells. The highest dose of DHEAS reduced IL-6 production by splenocytes from uninfected old mice by 75% while increasing their IL-2 secretion by nearly 50%. Thus immune dysfunction induced by ageing, even when exacerbated by murine retrovirus infection, was largely prevented by DHEAS

Curcumin is an in vivo inhibitor of angiogenesis.

Arbiser JL, Klauber N, Rohan R, et al.

Mol Med. 1998 Jun; 4(6):376-83.

BACKGROUND: Curcumin is a small-molecular-weight compound that is isolated from the commonly used spice turmeric. In animal models, curcumin and its derivatives have been shown to inhibit the progression of chemically induced colon and skin cancers. The genetic changes in carcinogenesis in these organs involve different genes, but curcumin is effective in preventing carcinogenesis in both organs. A possible explanation for this finding is that curcumin may inhibit angiogenesis. **MATERIALS AND METHODS:** Curcumin was tested for its ability to inhibit the proliferation of primary endothelial cells in the presence and absence of basic fibroblast growth factor (bFGF), as well as its ability to inhibit proliferation of an immortalized endothelial cell line. Curcumin and its derivatives were subsequently tested for their ability to inhibit bFGF-induced corneal neovascularization in

the mouse cornea. Finally, curcumin was tested for its ability to inhibit phorbol ester-stimulated vascular endothelial growth factor (VEGF) mRNA production. RESULTS: Curcumin effectively inhibited endothelial cell proliferation in a dose-dependent manner. Curcumin and its derivatives demonstrated significant inhibition of bFGF-mediated corneal neovascularization in the mouse. Curcumin had no effect on phorbol ester-stimulated VEGF production. CONCLUSIONS: These results indicate that curcumin has direct antiangiogenic activity in vitro and in vivo. The activity of curcumin in inhibiting carcinogenesis in diverse organs such as the skin and colon may be mediated in part through angiogenesis inhibition

Resveratrol, a natural product derived from grapes, is a new inducer of differentiation in human myeloid leukemias.

Asou H, Koshizuka K, Kyo T, et al.

Int J Hematol. 2002 Jun; 75(5):528-33.

A natural product, resveratrol (3,4,4'-trihydroxy-trans-stilbene), a phytoalexin found in grapes and other food products, is known as a cancer chemopreventive agent. We studied the in vitro biological activity of this compound by examining its effect on proliferation and differentiation in myeloid leukemia cell lines (HL-60, NB4, U937, THP-1, ML-1, Kasumi-1) and fresh samples from 17 patients with acute myeloid leukemia. Resveratrol (20 microM, 4 days) alone inhibited the growth in liquid culture of each of the 6 cell lines. Resveratrol (10 microM) enhanced the expression of adhesion molecules (CD11a, CD11b, CD18, CD54) in each of the cell lines except for Kasumi-1. Moreover, resveratrol (25 microM, 4 days) induced 37% of U937 cells to produce superoxide as measured by the ability to reduce nitroblue tetrazolium (NBT). The combination of resveratrol (10 microM) and all-trans-retinoic acid (ATRA) (50 nM, 4 days) induced 95% of the NB4 cells to become NBT-positive, whereas <1% and 12% of the cells became positive for NBT after a similar exposure to either resveratrol or ATRA alone, respectively. In U937 cells exposed to resveratrol (25 microM, 3 days), the binding activity of nuclear factor-kappaB (NFkappaB) protein was suppressed. Eight of 19 samples of fresh acute leukemia cells reduced NBT after exposure to resveratrol (20 microM, 4 days). Taken together, these findings show that resveratrol inhibits proliferation and induces differentiation of myeloid leukemia cells

The role of interferon as maintenance therapy in malignant lymphoma.

Aviles A.

Med Oncol. 1997 Sep; 14(3-4):153-7.

Interferon (IFN) is a biologic response modifier that has been employed in the treatment of malignant lymphomas with various degrees of success. In patients with low-grade lymphomas, IFN alone induced complete remissions in 17-62% of the patients. When used in combination with chemotherapy, prolongation of remission duration and survival has been reported. The best results have been reported when IFN was used as maintenance therapy in patients with minimal residual disease or complete remission. When used as maintenance treatment toxicity was mild with less than 5% of the patients discontinuing IFN treatment, and late side-effects have not been reported. The results obtained with IFN in patients with intermediate and high-grade lymphomas are disappointing. Complete remissions were observed in less than 10% of the patients and duration of remission and survival did not exceed 12 months. In contrast, promising results have been reported when IFN was used as maintenance treatment following bone marrow transplantation. In conclusion, IFN should be considered as part of the therapeutic process in patients with low-grade lymphomas, and in particular as a maintenance treatment following induction chemotherapy

Detrimental effect of cancer preventive phytochemicals silymarin, genistein and epigallocatechin 3-gallate on epigenetic events in human prostate carcinoma DU145 cells.

Bhatia N, Agarwal R.

Prostate. 2001 Feb 1; 46(2):98-107.

BACKGROUND: Targeting epigenetic events associated with autonomous growth of advanced prostate cancer (PCA) is a practical approach for its control, prevention, and treatment. Recently we showed that treatment of prostate carcinoma DU145 cells with cancer preventive flavonoid silymarin at 100-200 microM doses inhibits erbB1-Shc mitogenic signaling and modulates cell cycle regulators leading to a G1 arrest and inhibition of cell growth and anchorage-independent colony formation. Here, we asked the question whether these important findings could be extended to other cancer preventive flavonoids and isoflavones such as epigallocatechin 3-gallate (EGCG) and genistein. METHODS: DU145 cells were treated with similar doses (100-200 microM) of silymarin, genistein or EGCG, cell lysates prepared, and levels of activated signaling molecules (erbB1-Shc-ERK1/2) and cell cycle regulators (CDKs, CDKs, and cyclins) analyzed employing immunoprecipitation and/or immunoblotting techniques. Cell growth studies were done by cell counting during 5 days of treatment with these agents, and cell death was determined by Trypan blue staining. RESULTS: Treatment of cells with silymarin, genistein or EGCG at 100-200 microM resulted in a complete inhibition of TGFalpha-caused activation of erbB1 followed by a moderate to strong inhibition (10-90%) of Shc activation without an alteration in their protein levels. Silymarin and genistein, but not EGCG, also inhibited (10% to

complete) ERK1/2 activation suggesting that these agents impair erbB1-Shc-ERK1/2 signaling in DU145 cells. In other studies, silymarin, genistein or EGCG caused a strong induction of Cip1/p21 (up to 2.4-fold) and Kip1/p27 (up to 150-fold), and a strong decrease in CDK4 (40-90%) but had moderate effect on CDK2, and cyclins D1 and E. An enhanced level of CDKs also led to an increase in their binding to CDK4 and CDK2. Treatment of cells with silymarin, genistein or EGCG also resulted in 50-80% cell growth inhibition at lower doses, and complete inhibition at higher doses. In contrast to silymarin, higher doses of genistein showed cytotoxic effect causing 30-40% cell death. A more profound cytotoxic effect was observed with EGCG accounting for 50% cell death at lower doses and complete loss of viability at higher doses. CONCLUSIONS: These results suggest that similar to silymarin, genistein and EGCG also inhibit mitogenic signaling pathway(s) and alter cell cycle regulators, albeit at different levels, leading to growth inhibition and death of advanced and androgen-independent prostate carcinoma cells. More studies are, therefore, needed with these agents to explore their anti-carcinogenic potential against human prostate cancer

Effect of the protein tyrosine kinase inhibitor genistein on normal and leukaemic haemopoietic progenitor cells.

Carlo-Stella C, Regazzi E, Garau D, et al.

Br J Haematol. 1996 Jun; 93(3):551-7.

Receptor and nonreceptor protein tyrosine kinases (PTKs) play a key role in the control of normal and neoplastic cell growth. The availability of PTK inhibitors prompted us to evaluate the effects of genistein, a natural inhibitor of PTKs, on in vitro colony formation by normal multilineage colony-forming units (CFU-Mix), erythroid bursts (BFU-E), granulocyte-macrophage colony-forming units (CFU-GM), long-term culture-initiating cells (LTC-IC) and acute myelogenous leukaemia colony-forming units (CFU-AML). Continuous exposure of normal marrow and blood mononuclear non-adherent cells, blood CD34+CD

Selection of myeloid progenitors lacking BCR/ABL mRNA in chronic myelogenous leukemia patients after in vitro treatment with the tyrosine kinase inhibitor genistein.

Carlo-Stella C, Dotti G, Mangoni L, et al.

Blood. 1996 Oct 15; 88(8):3091-100.

Chronic myelogenous leukemia (CML) is a clonal disorder of the hematopoietic stem cell characterized by a chimeric BCR/ABL gene giving rise to a 210-kD fusion protein with dysregulated tyrosine kinase activity. We investigated the effect of genistein, a protein tyrosine kinase inhibitor, on the in vitro growth of CML and normal marrow-derived multi-potent (colony-forming unit-mix [CFU-Mix]), erythroid (burst-forming unit-erythroid [BFU-E]), and granulocyte-macrophage (colony-forming unit-granulocyte-macrophage [CFU-GM]) hematopoietic progenitors. Continuous exposure of CML and normal marrow to genistein induced a statistically significant and dose-dependent suppression of colony formation. Genistein doses causing 50% inhibition of CML and normal progenitors were not significantly different for CFU-Mix (27 $\mu\text{mol/L}$ v 23 $\mu\text{mol/L}$), BFU-E (31 $\mu\text{mol/L}$ v 29 $\mu\text{mol/L}$), and CFU-GM (40 $\mu\text{mol/L}$ v 32 $\mu\text{mol/L}$ v 32 $\mu\text{mol/L}$). Preincubation of CML and normal marrow with genistein (200 $\mu\text{mol/L}$ for 1 to 18 hours) induced a time-dependent suppression of progenitor cell growth, while sparing a substantial proportion of long-term culture-initiating cells (LTC-IC) from CML (range, 91% \pm 9% to 32% \pm 3%) and normal marrow (range, 85% \pm 8% to 38% \pm 9%). Analysis of individual CML colonies for the presence of the hybrid BCR/ABL mRNA by reverse transcription-polymerase chain reaction (RT-PCR) showed that genistein treatment significantly reduced the mean \pm SD percentage of marrow BCR/ABL+ progenitors both by continuous exposure (76% \pm 18% v 24% \pm 12%, $P < \text{or} = .004$) or preincubation (75% \pm 16% v 21% \pm 10%, $P < \text{or} = .002$) experiments. Preincubation with genistein reduced the percentage of leukemic LTC-IC from 87% \pm 12% to 37% \pm 12% ($P < \text{or} = .003$). Analysis of individual colonies by cytogenetics and RT-PCR confirmed that genistein-induced increase in the percentage of nonleukemic progenitors was not due to suppression of BCR/ABL transcription. Analysis of nuclear DNA fragmentation by DNA gel electrophoresis and terminal deoxynucleotidyl transferase assay showed that preincubation of CML mononuclear and CD34+ cells with genistein induced significant evidence of apoptosis. These observations show that genistein is capable of (1) exerting a strong antiproliferative effect on CFU-Mix, BFU-E, and CFU-GM while sparing the more primitive LTC-IC and (2) selecting benign hematopoietic progenitors from CML marrow, probably through an apoptotic mechanism

Medical history risk factors for non-Hodgkin's lymphoma in older women.

Cerhan JR, Wallace RB, Folsom AR, et al.

J Natl Cancer Inst. 1997 Feb 19; 89(4):314-8.

BACKGROUND: It has been suggested that certain medical conditions and drug exposures might suppress the immune system and increase the risk of developing non-Hodgkin's lymphoma (NHL). PURPOSE: We investigated whether specific medical conditions and drug exposures were associated with the risk of NHL in a cohort of older women who were enrolled in the Iowa Women's Health Study. METHODS: A cohort of 41837 women, 55-69 years of age at baseline, was followed prospectively for

the development of cancer from 1986 through 1992. These women had completed a baseline questionnaire in January 1986 that inquired about the occurrence and age at onset of specific medical conditions, about family history of cancer, and about the use of selected medications. Follow-up questionnaires were mailed to the women in 1987, 1989, and 1992. Incident cancers and deaths were ascertained through linkages to state and national databases. For most analyses, women with a self-reported history of cancer at baseline (n = 3903) were excluded. Relative risks (RRs) and 95% confidence intervals (CIs), adjusted for age or for age and other variables, were used as a measure of the association between NHL and medical history factors. Reported P values are two-sided. RESULTS: One hundred fourteen incident cases of NHL were identified in the cohort during follow-up. A history of adult-onset diabetes mellitus (i.e., first diagnosed after the age of 30 years) was associated with an increased risk of developing NHL (age-adjusted RR = 2.18; 95% CI = 1.22-3.90). In addition, there was an association between the duration of adult-onset diabetes and increasing risk of NHL (P for trend = .004), with an age-adjusted RR of 2.90 (95% CI = 1.07-7.90) for women with a diagnosis of diabetes for 15 or more years compared with women with no diagnosis of diabetes. Women with a history of blood transfusion were also at increased risk for the development of NHL (age-adjusted RR = 1.95; 95% CI = 1.33-2.85). The risk estimates for diabetes and transfusion history were independent of each other and were not changed substantially after adjustment for other risk factors. History of a previous cancer (excluding hematopoietic and lymphatic cancers) was associated with an increased risk of NHL (age-adjusted RR = 1.92; 95% CI = 1.21-3.06); this risk estimate was attenuated somewhat after adjustment for a history of diabetes, transfusion history, and other major risk factors (RR = 1.66; 95% CI = 1.02-2.69). No statistically significant associations were found between NHL and a history of chronic colitis, nonestrogen steroid use, use of exogenous estrogens, or use of thyroid medications. CONCLUSIONS AND IMPLICATIONS: A history of adult-onset diabetes mellitus, blood transfusion, and a history of cancer (or its treatment) appear to be independent risk factors for NHL in older women

Pseudoepitheliomatous hyperplasia in cutaneous T-cell lymphoma. A clinical, histopathological and immunohistochemical study with particular interest in epithelial growth factor expression. The French Study Group on Cutaneous Lymphoma.

Courville P, Wechsler J, Thomine E, et al.

Br J Dermatol. 1999 Mar; 140(3):421-6.

Pseudoepitheliomatous hyperplasia has occasionally been reported in cutaneous T-cell lymphoma (CTCL). This association raises the question of the relationship between epidermal hyperplasia and the lymphomatous infiltrate. Because epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-alpha) have been demonstrated to be involved in epidermal proliferation through binding to EGF receptor (EGFr), we tested the hypothesis that these cytokines could be secreted by lymphomatous cells, and induce the overlying pseudoepitheliomatous hyperplasia. The purposes of this study were: (i) to describe the clinical and immunohistological features of pseudoepitheliomatous hyperplasia; (ii) to determine its frequency in a large series of CTCLs; and (iii) to evaluate the expression of EGF, TGF-alpha and EGFr in CTCL with or without pseudoepitheliomatous hyperplasia. Eleven cases of CTCL with pseudoepitheliomatous hyperplasia were collected from a series of 353 cases of cutaneous lymphoma registered from 1990 to 1996. They consisted of eight of 28 (28.5%) CD30+ large T-cell lymphomas and three of 148 (2%) cases of mycosis fungoides. Epidermal expression of EGF, EGFr and TGF-alpha was stronger in CTCL than in control normal human skin. Lymphomatous T cells expressed EGF and TGF-alpha whereas no expression of these cytokines could be detected in cutaneous and nodal B-cell lymphomas, nor in a normal lymph node. In addition, epidermal expression of EGFr was stronger in CTCL with pseudoepitheliomatous hyperplasia than in control cases of CTCL without pseudoepitheliomatous hyperplasia, suggesting that these cytokines, in association with other factors, are probably involved in the epidermal hyperplasia observed in some cases of CTCL

Fatty acid modulation of endothelial activation.

De Caterina R, Liao JK, Libby P.

Am J Clin Nutr. 2000 Jan; 71(1 Suppl):213S-23S.

Dietary balance of long-chain fatty acids may influence processes involving leukocyte-endothelial interactions, such as atherogenesis and inflammation, that involve increased endothelial expression of leukocyte adhesion molecules, or endothelial activation. We compared the ability of various saturated, monounsaturated, and polyunsaturated fatty acids to modulate endothelial activation. Consumption of the n-3 fatty acid docosahexaenoic acid (DHA; 22:6n-3) reduced endothelial expression of vascular cell adhesion molecule 1 (VCAM-1), E-selectin, intercellular adhesion molecule 1 (ICAM-1), interleukin 6 (IL-6), and IL-8 in response to IL-1, IL-4, tumor necrosis factor, or bacterial endotoxin, with a half-maximal inhibitory concentration (IC(50)) of 1-25 micromol, ie, in the range of nutritionally achievable plasma concentrations. The magnitude of this effect paralleled its incorporation into cellular phospholipids. DHA also reduced the adhesion of human monocytes and monocytic U937 cells to cytokine-stimulated endothelial cells. These effects were accompanied by a reduction in VCAM-1 messenger RNA, indicating a pretranslational effect. To assess structural fatty acid determinants of VCAM-1 inhibitory activity, we compared various saturated, monounsaturated, and n-6 and n-3 polyunsaturated fatty acids for their VCAM-1 inhibitory activity. Saturated fatty acids did not inhibit cytokine-induced expression of adhesion molecules. However, a progressive increase in inhibitory activity

was observed with dietary intake of fatty acids with the same chain length but increasing double bonds, ie, from monounsaturated to n-6 and, further, to n-3 fatty acids. Thus, the greater number of double bonds seems critical for the greater activity of n-3 compared with n-6 fatty acids in inhibiting endothelial activation. These properties are likely to be relevant to the antiatherogenic and antiinflammatory properties of n-3 fatty acids

Expression of Retinoid X Receptor alpha is increased upon monocytic cell differentiation.

Defacque H, Commes T, Legouffe E, et al.

Biochem Biophys Res Commun. 1996 Mar 18; 220(2):315-22.

1 alpha, 25-Dihydroxyvitamin D₃ (VD) is a potent inducer of monocytic differentiation of both normal and leukemic cells. Its effects are mediated by its nuclear receptor (VDR). Efficient gene activation requires the heterodimerization of VDR with Retinoid X Receptors (RXR). In the present study using specific antibodies, we analyzed the expression of the RXR alpha protein in blood mononuclear cells from acute myeloid patients (AML) (10 cases) and from myelomonocytic cell lines arrested at different stages of differentiation. We observed that the RXR alpha expression increased during myelomonocytic differentiation, since the highest levels were found in AML samples and in myelomonocytic cell lines having the highest amounts of monocytic precursors. We also demonstrated that fresh leukemic cells, whatever their stage of differentiation, as well as myelomonocytic cell lines, respond to VD by an increase in RXR alpha levels. Combinations of all-trans retinoic acid (RA) and VD, in some cases, increased this effect. This response suggests the involvement of RXR alpha in monocytic differentiation upon VD treatment

Combination of a potent 20-epi-vitamin D₃ analogue (KH 1060) with 9-cis-retinoic acid irreversibly inhibits clonal growth, decreases bcl-2 expression, and induces apoptosis in HL-60 leukemic cells.

Elstner E, Linker-Israeli M, Umiel T, et al.

Cancer Res. 1996 Aug 1; 56(15):3570-6.

All-trans retinoic acid (RA) is the first highly effective differentiation-inducing agent for remission induction in patients with acute promyelocytic leukemia. However, remissions are short-lived because the treatment fails to induce complete differentiation and fails to eradicate the malignant clone. To eliminate rapidly the malignant clone, in analogy with aggressive chemotherapy, the combination of potent differentiation- and apoptosis-inducing drugs working through different receptors and signal pathways may be useful. The active form of vitamin D₃ (1,25-dihydroxyvitamin D₃; 1,25(OH)₂D₃) inhibits proliferation and induces differentiation of myeloid leukemic cells. The 9-cis-RA, unlike all-trans-RA which binds only retinoic acid receptors, is a high affinity ligand for both retinoic acid receptors and retinoid X receptors. The aim of this study was to evaluate the therapeutic potential of combining a vitamin D₃ analogue, 20-epi-22-oxa-24a,26a,27a-tri-homo-1alpha,25(OH)₂D₃ (KH 1060), which belongs to the family of potent 20-epi-1,25(OH)₂D₃ analogues, with 9-cis-RA by assessing their effects on the proliferation, differentiation, and apoptosis of the human leukemia cell line HL-60 in vitro. Our data show that KH 1060 alone is a very potent inhibitor of clonal proliferation of HL-60, but this effect is reversible, and that 9-cis-RA alone is a weak inhibitor of clonal proliferation of HL-60 cells. In contrast, the combination of KH 1060 and 9-cis-RA synergistically and irreversibly inhibited the clonal proliferation of HL-60 cells and induced apoptosis, as detected by morphological changes and DNA fragmentation. This combination also affected the expression of apoptosis-related genes. The bcl-2 protein became nearly undetectable, and expression of bax protein increased slightly (the bax:bcl-2 ratio was 14-fold higher than in untreated cells). Differentiation of treated HL-60 cells was assessed by their ability to produce superoxide, as measured by reduction of nitro blue tetrazolium, positive staining for alpha-naphthyl acetate esterase, phagocytosis, morphology, and analysis of membrane-bound differentiation markers with two-color immunofluorescence. Treatment with the combination of KH 1060 and 9-cis-RA was a potent inducer of differentiation of HL-60, with the cells developing a myelomonocytic phenotype. In summary, our data demonstrate that the combination of both KH 1060 and 9-cis-RA irreversibly and synergistically inhibited clonal growth, induced differentiation and apoptosis of HL-60 cells concomitantly with a very marked decreased expression of bcl-2, and increased the bax:bcl-2 ratio. This drug combination may have important therapeutic significance

Resveratrol blocks interleukin-1beta-induced activation of the nuclear transcription factor NF-kappaB, inhibits proliferation, causes S-phase arrest, and induces apoptosis of acute myeloid leukemia cells.

Estrov Z, Shishodia S, Faderl S, et al.

Blood. 2003 Aug 1; 102(3):987-95.

Resveratrol, an edible polyphenolic stilbene, has been reported to possess substantial antileukemic activities in different leukemia cell lines. We investigated whether resveratrol is active against fresh acute myeloid leukemia (AML) cells and its mechanism of action. Because interleukin 1beta (IL-1beta) plays a key role in proliferation of AML cells, we first tested the effect of resveratrol on the AML cell lines OC1M2 and OCI/AML3, both of which produce IL-1beta and proliferate in response to it.

Resveratrol inhibited proliferation of both cell lines in a dose-dependent fashion (5-75 microM) by arresting the cells at S phase, thus preventing their progression through the cell cycle; IL-1beta partially reversed this inhibitory effect. Resveratrol significantly reduced production of IL-1beta in OCIM2 cells. It also suppressed the IL-1beta-induced activation of transcription factor nuclear factor kappaB (NF-kappaB), which modulates an array of signals controlling cellular survival, proliferation, and cytokine production. Indeed, incubation of OCIM2 cells with resveratrol resulted in apoptotic cell death. Because caspase inhibitors Ac-DEVD-CHO or z-DEVD-FMK partially reversed the antiproliferative effect of resveratrol, we tested its effect on the caspase pathway and found that resveratrol induced the activation of the cysteine protease caspase 3 and subsequent cleavage of the DNA repair enzyme poly (adenosine diphosphate [ADP]-ribose) polymerase. Finally, resveratrol suppressed colony-forming cell proliferation of fresh AML marrow cells from 5 patients with newly diagnosed AML in a dose-dependent fashion. Taken together, our data showing that resveratrol is an effective in vitro inhibitor of AML cells suggest that this compound may have a role in future therapies for AML

Interleukin-6 and interleukin-10 levels in chronic lymphocytic leukemia: correlation with phenotypic characteristics and outcome.

Fayad L, Keating MJ, Reuben JM, et al.

Blood. 2001 Jan 1; 97(1):256-63.

The objective of this study was to examine the correlation between serum interleukin-6 (IL-6) and IL-10 levels and outcome in chronic lymphocytic leukemia (CLL). Serum IL-6 and IL-10 levels were measured by enzyme-linked immunoabsorbent assays from 159 and 151 CLL patients, respectively, and from healthy control subjects (n = 55 [IL-6]; n = 37 [IL-10]). Cytokine levels were correlated with clinical features and survival. Serum IL-6 levels were higher in CLL patients (median, 1.45 pg/mL; range, undetectable to 110 pg/mL) than in control subjects (median, undetectable; range, undetectable to 4.30 pg/mL) (P <.0001). Serum IL-10 levels were higher in CLL patients (median, 5.04 pg/mL; range, undetectable to 74 pg/mL) than in normal volunteers (median, undetectable; range, undetectable to 13.68 pg/mL) (P <.00001). Assays measuring both Epstein-Barr virus-derived and human IL-10 yielded higher values than assays measuring primarily human IL-10 (P <.05). Patients with elevation of serum IL-6 or IL-10 levels, or both, had worse median and 3-year survival (log rank P <.001) and unfavorable characteristics (prior treatment, elevated beta(2)-microglobulin or lactate dehydrogenase, or Rai stage III or IV). Elevated IL-6 and IL-10 levels were independent prognostic factors for survival when analyzed individually or in combination (Cox regression analysis). However, if beta(2)-microglobulin was incorporated into the analysis, it was selected as an independent prognostic feature, and IL-6/IL-10 were no longer selected. In patients with CLL, serum IL-6 and IL-10 (viral and human) levels are elevated and correlate with adverse disease features and short survival. In multivariate analysis, however, beta(2)-microglobulin is the most important prognostic factor

High levels of vascular endothelial growth factor receptor-2 correlate with shortened survival in chronic lymphocytic leukemia.

Ferrajoli A, Manshouri T, Estrov Z, et al.

Clin Cancer Res. 2001 Apr; 7(4):795-9.

Vascular endothelial growth factor receptor-2 (VEGFR-2), also termed KDR, is a high-affinity vascular endothelial growth factor (VEGF) receptor. VEGFR-2 plays a role in de novo blood vessel formation and hematopoietic cell development. Recently, we found that chronic lymphocytic leukemia (CLL) cells express high levels of VEGF. Therefore, we sought to investigate the role of VEGFR-2 in CLL. Using Western blot analysis, we first determined that VEGFR-2 is present in peripheral blood CLL cells. We then quantified the cellular levels of VEGFR-2 protein using a solid-phase radioimmunoanalysis in peripheral blood cells from 216 patients with CLL. As control, we used peripheral blood mononuclear cells (PBMNCs) from 31 hematologically normal individuals. The median of VEGFR-2 levels detected in the control samples was assigned a value of 1.0, and VEGFR-2 protein levels were normalized to the control median value. The median level of VEGFR-2 in CLL cells was 1.57. Patients with VEGFR-2 levels higher than 1.57 had elevated lymphocyte counts, severe anemia, elevated beta(2)-microglobulin and advanced-stage disease. Elevated VEGFR-2 levels were also associated with statistically significantly shorter survival (35.4 versus 60.1 months; P < 0.01). Our data indicate that cellular VEGFR-2 levels may serve as a prognostic factor in CLL. Further studies should investigate the biological implications of these findings and the effect of the interaction between VEGF and VEGFR-2 on CLL cell proliferation

(R)-alpha-lipoic acid-supplemented old rats have improved mitochondrial function, decreased oxidative damage, and increased metabolic rate.

Hagen TM, Ingersoll RT, Lykkesfeldt J, et al.

FASEB J. 1999 Feb; 13(2):411-8.

A diet supplemented with (R)-lipoic acid, a mitochondrial coenzyme, was fed to old rats to determine its efficacy in reversing the

decline in metabolism seen with age. Young (3 to 5 months) and old (24 to 26 months) rats were fed an AIN-93M diet with or without (R)-lipoic acid (0.5% w/w) for 2 wk, killed, and their liver parenchymal cells were isolated. Hepatocytes from untreated old rats vs. young controls had significantly lower oxygen consumption ($P < 0.03$) and mitochondrial membrane potential. (R)-Lipoic acid supplementation reversed the age-related decline in O_2 consumption and increased ($P < 0.03$) mitochondrial membrane potential. Ambulatory activity, a measure of general metabolic activity, was almost threefold lower in untreated old rats vs. controls, but this decline was reversed ($P < 0.005$) in old rats fed (R)-lipoic acid. The increase of oxidants with age, as measured by the fluorescence produced on oxidizing 2',7'-dichlorofluorescein, was significantly lowered in (R)-lipoic acid supplemented old rats ($P < 0.01$). Malondialdehyde (MDA) levels, an indicator of lipid peroxidation, were increased fivefold with age in cells from unsupplemented rats. Feeding rats the (R)-lipoic acid diet reduced MDA levels markedly ($P < 0.01$). Both glutathione and ascorbic acid levels declined in hepatocytes with age, but their loss was completely reversed with (R)-lipoic acid supplementation. Thus, (R)-lipoic acid supplementation improves indices of metabolic activity as well as lowers oxidative stress and damage evident in aging

Signal transduction by basic fibroblast growth factor in rat osteoblastic Py1a cells.

Hurley MM, Marcello K, Abreu C, et al.

J Bone Miner Res. 1996 Sep; 11(9):1256-63.

Basic fibroblast growth factor (bFGF) is a potent mitogen for bone. In this study, we utilized the clonal rat osteoblastic cell line, Py1a, to examine signal transduction by bFGF and to determine the role of mitogen activated protein kinases (MAPK) and induction of c-fos mRNA in the mitogenic response to bFGF. Stimulation of [3 H]thymidine incorporation (TDR) into DNA by bFGF was determined in the presence of phorbol myristate acetate (PMA) to down-regulate the protein kinase C (PKC) pathway, genistein, an inhibitor of tyrosine kinase and H-7, a PKC inhibitor, bFGF 10(-8) M and PMA 10(-7) M increased TDR by 242 and 245%, respectively. Treatment with bFGF or PMA for 5 or 30 minutes increased tyrosine phosphorylation of multiple proteins, and immunoblotting with MAPK-specific antibody revealed that two of these bands were the 42 and 44 kD isoforms of MAPK. PMA and bFGF induced c-fos mRNA expression at 30 minutes. Genistein at 10 micrograms/ml blocked the mitogenic effect of bFGF and partially inhibited the mitogenic effect of PMA. Genistein at 100 micrograms/ml also blocked both bFGF- and PMA-induced increases in c-fos mRNA. A 24 h pretreatment with PMA at 10(-7) M inhibited the mitogenic response, tyrosine phosphorylation of MAPK, and induction of c-fos mRNA subsequent to the addition of PMA, but not bFGF. H-7 at 50 microM blocked bFGF-induced mitogenesis and c-fos induction, but did not inhibit bFGF-induced tyrosine phosphorylation of MAPK. In this study, we show that the signaling pathway of bFGF and PMA are similar in that they both induce tyrosine phosphorylation of MAP kinases and activate c-fos. However, the signaling pathways ultimately diverge in that once the PKC pathway is down-regulated by PMA pretreatment or blocked by the PKC inhibitor H-7, tyrosine phosphorylation of MAP kinase, c-fos induction, and the mitogenic effect of PMA is blocked. In contrast, down-regulation of the PKC pathway inhibits c-fos and the mitogenic response to bFGF, but not bFGF's effects on tyrosine phosphorylation of MAP kinase

Modulation of cytokine production by dehydroepiandrosterone (DHEA) plus melatonin (MLT) supplementation of old mice.

Inserra P, Zhang Z, Ardestani SK, et al.

Proc Soc Exp Biol Med. 1998 May; 218(1):76-82.

Tissue levels of the antioxidants melatonin (MLT) and dehydroepiandrosterone (DHEA) decline with age, and this decline is correlated with immune dysfunction. The aim of the current study is to determine whether hormone supplementation with MLT and DHEA together would synergize to reverse immune senescence. Old (16.5 months) female C57BL/6 mice were treated with DHEA, MLT, or DHEA + MLT. As expected, splenocytes were significantly ($P < 0.05$) higher in old mice as compared to young mice. DHEA, MLT, and DHEA + MLT significantly ($P < 0.005$) increased B cell proliferation in young mice. However, only MLT and DHEA + MLT significantly ($P < 0.05$) increased B cell proliferation in old mice. DHEA, MLT, and DHEA + MLT help to regulate immune function in aged female C57BL/6 mice by significantly ($P < 0.05$) increasing Th1 cytokines, IL-2, and IFN-gamma or significantly ($P < 0.05$) decreasing Th2 cytokines, IL-6, and IL-10, thus regulating cytokine production. DHEA and MLT effectively modulate suppressed Th1 cytokine and elevated Th2 cytokine production; however, their combined use produced only a limited additive effect

Curcumin induces a p53-dependent apoptosis in human basal cell carcinoma cells.

Jee SH, Shen SC, Tseng CR, et al.

J Invest Dermatol. 1998 Oct; 111(4):656-61.

Curcumin, a potent antioxidant and chemopreventive agent, has recently been found to be capable of inducing apoptosis in human hepatoma and leukemia cells by way of an elusive mechanism. Here, we demonstrate that curcumin also induces

apoptosis in human basal cell carcinoma cells in a dose- and time-dependent manner, as evidenced by internucleosomal DNA fragmentation and morphologic change. In our study, consistent with the occurrence of DNA fragmentation, nuclear p53 protein initially increased at 12 h and peaked at 48 h after curcumin treatment. Prior treatment of cells with cycloheximide or actinomycin D abolished the p53 increase and apoptosis induced by curcumin, suggesting that either de novo p53 protein synthesis or some proteins synthesis for stabilization of p53 is required for apoptosis. In electrophoretic mobility gel-shift assays, nuclear extracts of cells treated with curcumin displayed distinct patterns of binding between p53 and its consensus binding site. Supportive of these findings, p53 downstream targets, including p21(CIP1/WAF1) and Gadd45, could be induced to localize on the nucleus by curcumin with similar p53 kinetics. Moreover, we immunoprecipitated extracts from basal cell carcinoma cells with different anti-p53 antibodies, which are known to be specific for wild-type or mutant p53 protein. The results reveal that basal cell carcinoma cells contain exclusively wild-type p53; however, curcumin treatment did not interfere with cell cycling. Similarly, the apoptosis suppressor Bcl-2 and promoter Bax were not changed with the curcumin treatment. Finally, treatment of cells with p53 antisense oligonucleotide could effectively prevent curcumin-induced intracellular p53 protein increase and apoptosis, but sense p53 oligonucleotide could not. Thus, our data suggest that the p53-associated signaling pathway is critically involved in curcumin-mediated apoptotic cell death. This evidence also suggests that curcumin may be a potent agent for skin cancer prevention or therapy

EGCG, a major component of green tea, inhibits tumour growth by inhibiting VEGF induction in human colon carcinoma cells.

Jung YD, Kim MS, Shin BA, et al.

Br J Cancer. 2001 Mar 23; 84(6):844-50.

Catechins are key components of teas that have antiproliferative properties. We investigated the effects of green tea catechins on intracellular signalling and VEGF induction in vitro in serum-deprived HT29 human colon cancer cells and in vivo on the growth of HT29 cells in nude mice. In the in vitro studies, (-)-epigallocatechin gallate (EGCG), the most abundant catechin in green tea extract, inhibited Erk-1 and Erk-2 activation in a dose-dependent manner. However, other tea catechins such as (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG), and (-)-epicatechin (EC) did not affect Erk-1 or 2 activation at a concentration of 30 microM. EGCG also inhibited the increase of VEGF expression and promoter activity induced by serum starvation. In the in vivo studies, athymic BALB/c nude mice were inoculated subcutaneously with HT29 cells and treated with daily intraperitoneal injections of EC (negative control) or EGCG at 1.5 mg day⁻¹mouse⁻¹ starting 2 days after tumour cell inoculation. Treatment with EGCG inhibited tumour growth (58%), microvessel density (30%), and tumour cell proliferation (27%) and increased tumour cell apoptosis (1.9-fold) and endothelial cell apoptosis (3-fold) relative to the control condition (P < 0.05 for all comparisons). EGCG may exert at least part of its anticancer effect by inhibiting angiogenesis through blocking the induction of VEGF

From vitamin to Vesanoid: systemic retinoids for the new millennium.

Kerr PE, DiGiovanna JJ.

Med Health R I. 2001 Jul; 84(7):228-31.

Retinoids are a fascinating class of compounds that exert control over cellular function from the time of conception to death. They play a critical role in such vital processes as fetal morphogenesis, cellular differentiation and apoptosis. Over the years synthetic retinoids have provided dermatologists with a spectrum of medications that have profound therapeutic effects on a variety of recalcitrant skin disorders. Moreover, retinoids are an expanding component of the treatment arsenal against hematologic and solid malignancies. Retinoids are poised to offer exciting new therapeutic options in the field of endocrinology for the treatment of diabetes and lipid disorders. Researchers and clinicians are only beginning to unveil the therapeutic potential of this class of medications. The development of new retinoid compounds targeting specific receptors promises a wealth of new therapies for the new millennium

Curcumin, an antioxidant and anti-tumor promoter, induces apoptosis in human leukemia cells.

Kuo ML, Huang TS, Lin JK.

Biochim Biophys Acta. 1996 Nov 15; 1317(2):95-100.

Curcumin, widely used as a spice and coloring agent in food, possesses potent antioxidant, anti-inflammatory and anti-tumor promoting activities. In the present study, curcumin was found to induce apoptotic cell death in promyelocytic leukemia HL-60 cells at concentrations as low as 3.5 micrograms/ml. The apoptosis-inducing activity of curcumin appeared in a dose- and time-dependent manner. Flow cytometric analysis showed that the hypodiploid DNA peak of propidium iodide-stained nuclei appeared at 4 h after 7 micrograms/ml curcumin treatment. The apoptosis-inducing activity of curcumin was not affected by

cycloheximide, actinomycin D, EGTA, W7 (calcium orthovanadate, or genistein). By contrast, an endonuclease inhibitor ZnSO₄ and proteinase inhibitor N-tosyl-L-lysine chloro-methyl ketone (TLCK) could markedly abrogate apoptosis induced by curcumin, whereas 12-O-tetradecanoylphorbol-13-acetate (TPA) had a partial effect. The antioxidants, N-acetyl-L-cysteine (NAC), L-ascorbic acid, alpha-tocopherol, catalase and superoxide dismutase, all effectively prevented curcumin-induced apoptosis. This result suggested that curcumin-induced cell death was mediated by reactive oxygen species. Immunoblot analysis showed that the level of the antiapoptotic protein Bcl-2 was decreased to 30% after 6 h treatment with curcumin, and was subsequently reduced to 20% by a further 6 h treatment. Furthermore, overexpression of bcl-2 in HL-60 cells resulted in a delay of curcumin-treated cells entering into apoptosis, suggesting that bcl-2 plays a crucial role in the early stage of curcumin-triggered apoptotic cell death

1-O-Hexadecyl-2-methoxy-glycero-3-phosphatidylcholine? a methoxy ether lipid inhibiting platelet activating factor-induced platelet aggregation and neutrophil oxidative metabolism.

LeBlanc K.

Biochem Pharmacol. 1995; 49(11):1577-82.

Effects of cis-unsaturated fatty acids on doxorubicin sensitivity in P388/DOX resistant and P388 parental cell lines.

Liu QY, Tan BK.

Life Sci. 2000; 67(10):1207-18.

It has been reported that several cis-unsaturated fatty acids (c-UFAs) could increase doxorubicin (DOX) accumulation in cancer cells and hence elevate its cytotoxicity. However, some researchers showed that c-UFA pretreatment did not affect its cytotoxicity in special cell lines. It is possible that the different results occurred due to different cellular characteristics. We hypothesized that c-UFA treatment might modulate the activities of some antioxidant enzymes to affect the resistance of cells to DOX. In the present study, we examined how c-UFA pretreatment affected DOX cytotoxicity on mouse leukemia cell line, P388, and its resistant subline, P388/DOX, which we found to have significantly higher glutathione peroxidase (GPx) activity as well as P-glycoprotein (p-gp) overexpression. We chose two c-UFAs, gamma-linolenic acid (GLA) (18:3n-6) and docosahexaenoic acid (DHA) (22:6n-3). Cytotoxicity was measured by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) and trypan blue exclusion assays. DOX accumulation and p-gp expression were measured by flow cytometry. The activities of catalase (CAT), superoxide dismutase (SOD), glutathione S-transferase (GST), and GPx were determined for both cell lines with and without treatment with GLA or DHA. Significant DOX accumulation occurred in both cell lines with GLA or DHA pretreatment, but without any change in p-gp expression in either cell line. Sensitivity to DOX cytotoxicity was improved by GLA or DHA pretreatment in P388/DOX in which only SOD activity was significantly increased, but not in the parental cell line P388 in which both SOD and CAT were significantly increased by the pretreatment. However, combined pretreatment of GLA or DHA with antioxidants, pyrrolidinedithiocarbamate (PDTC) or Vitamin C, could sensitize not only P388/DOX but also P388 cells to DOX. We conclude that the effects of c-UFA pretreatment on the sensitivity of cancer cells to DOX not only depend on the change in drug accumulation but also the change in the levels of antioxidant enzyme activities, and suggest that combined administration of c-UFAs, antioxidants, and DOX may be more effective in treating leukemia

Age-associated decline in ascorbic acid concentration, recycling, and biosynthesis in rat hepatocytes--reversal with (R)-alpha-lipoic acid supplementation.

Lykkesfeldt J, Hagen TM, Vinarsky V, et al.

FASEB J. 1998 Sep; 12(12):1183-9.

Ascorbic acid recycling from dehydroascorbic acid and biosynthesis from gulono-1,4-lactone were used as measures of cellular response capacity to increased oxidative stress induced by tert-butylhydroperoxide. The hepatic ascorbic acid concentration was 54% lower in cells from old rats when compared to cells isolated from young rats (P<0.0005). Freshly isolated hepatocytes from old rats exhibited a significantly decreased ascorbic acid recycling capacity in response to oxidative stress (P<0.005) compared to cells from young rats. Ascorbic acid synthesis in these cells from old animals was unaffected by various concentrations of tert-butylhydroperoxide, but amounted to only approximately half of the biosynthetic rate when compared to cells from young animals (P<0.001). Cells from young animals were not significantly affected by the tert-butylhydroperoxide treatments. The results demonstrate a declining ability with age to respond to increased oxidative stress. (R)-alpha-Lipoic acid, a mitochondrial coenzyme, is a powerful antioxidant. A two-week dietary supplementation of old animals with 0.5% (R)-alpha-lipoic acid prior to cell isolation almost completely reversed the age-associated effects on ascorbic acid concentration (P<0.0001), recycling (P<0.05) and biosynthesis after oxidative stress. These results provide further evidence for the potential of alpha-lipoic acid in treatment of diseases related to oxidative stress. Furthermore, the study extends the value of ascorbic acid as a biomarker of oxidative stress

Treatment with all-trans retinoic acid in acute promyelocytic leukemia reduces early deaths in children.

Mann G, Reinhardt D, Ritter J, et al.

Ann Hematol. 2001 Jul; 80(7):417-22.

All-trans retinoic acid (ATRA) is a known inducer of differentiation in acute promyelocytic leukemia. To improve the outcome of children with acute promyelocytic leukemia, ATRA has been applied since 1994 as an additional induction element in the AML-BFM 93 study. In a retrospective study, we compared 22 children treated with ATRA (median age: 9.3 years; range: 1.8-16.3) with 22 patients receiving conventional therapy (median age: 12.3 years; range: 3.2-16.7). Twenty-one of the children achieved complete remission. Only one patient died early from bleeding complications after 3 days administration of ATRA. In the control group, seven early deaths occurred (Fisher exact test; $p < 0.04$). Two children died from intracerebral hemorrhages. Two patients suffered from sepsis during aplasia after induction therapy, and one child did not respond to treatment. The 5-year overall survival (OS) and event-free survival (EFS) of the children who received ATRA followed by chemotherapy were significantly better compared with conventionally treated children [OS: 0.87 ± 0.09 vs 0.45 ± 0.11 , p (log rank) < 0.003 ; EFS: 0.76 ± 0.11 vs 0.43 ± 0.11 , p (log rank) < 0.02]; the median observation time was 2.8 years (19-76 months). However, nearly all children suffered from common side effects such as headache, fever, joint, muscle and bone pain, weight gain, or dermatitis. In three patients, a retinoic acid syndrome was observed. Interruption of ATRA treatment and application of dexamethasone, necessary in 12 children, controlled the adverse effects. ATRA treatment could be resumed in 18 patients. In conclusion, ATRA treatment during induction could avoid early deaths in children with acute promyelocytic leukemia with considerable but manageable toxic side effects

The role of interferon in the therapy of malignant lymphoma.

McLaughlin P.

Biomed Pharmacother. 1996; 50(3-4):140-8.

As a single agent, interferon-alpha (IFN-alpha) can induce remissions, mostly partial, in a large fraction of patients with indolent lymphomas, including the low grade B-cell lymphomas and cutaneous T-cell lymphoma. In aggressive lymphomas, IFN has minimal activity, and in Hodgkin's disease the limited available experience suggests only modest activity. In indolent B-cell lymphomas, IFN has been integrated with chemotherapy in several large trials: the majority of these trials indicate a favorable impact on failure-free survival; a survival benefit of IFN has been reported by the French-Belgian group. Updated results are now available from a previously reported trial from the MD Anderson Cancer Center that also indicate an apparent survival benefit when IFN is used in conjunction with chemotherapy in patients with indolent B-cell lymphoma

In vivo assessment of NF-KB inhibitors as chemosensitizers: Study 4967. Paper Presented at the Annual Meeting of the American Association for Cancer Research.

Michaels S. BDM.

2001; March 24-28, 2001 Study 4967

The in vitro effects of all-trans-retinoic acid and hematopoietic growth factors on the clonal growth and self-renewal of blast stem cells in acute promyelocytic leukemia.

Miyauchi J, Inatomi Y, Ohyashiki K, et al.

Leuk Res. 1997 Apr; 21(4):285-94.

All-trans-retinoic acid (ATRA) has been used as a potent therapeutic agent to induce differentiation of acute promyelocytic leukemia (APL) cells, and granulocyte colony-stimulating factor (G-CSF) has been reported to enhance this effect of ATRA in vitro. We investigated the effects of ATRA and three myeloid growth factors, including G-CSF, on the growth of the leukemic stem cells of 10 APL patients. G-CSF was the most powerful stimulator of leukemic colony formation in five out of 10 patients, but was neither the major stimulant of self-renewal of the blast stem cells nor an inducer of maturation. In contrast, ATRA was highly effective in inducing morphological maturation of leukemic promyelocytes, but variable results were obtained in regard to its effects on the growth of blast stem cells: ATRA suppressed both clonal growth and self-renewal in some patients, but was inactive or even had stimulating effects in the other patients. Similar variable effects were observed with the combination of ATRA and G-CSF. These findings indicate that the differentiation-inducing effect of ATRA is not always associated with growth inhibition of leukemic stem cells in vitro and justify the use of chemotherapy in conjunction with ATRA in the treatment of APL

Suppression of protooncogene c-fos expression by antioxidant dihydrolipoic acid.

Mizuno M, Packer L.

Methods Enzymol. 1995; 252:180-6.

Hypoxic induction of human vascular endothelial growth factor expression through c-Src activation.

Mukhopadhyay D, Tsiokas L, Zhou XM, et al.

Nature. 1995 Jun 15; 375(6532):577-81.

Angiogenesis, the formation of new microvasculature by capillary sprouting, is crucial for tumour development. Hypoxic regions of solid tumours produce the powerful and directly acting angiogenic protein VEGF/VPF (vascular endothelial growth factor/vascular permeability factor). We now investigate the signal transduction pathway involved in hypoxic induction of VEGF expression. Hypoxia is known to induce a tyrosine kinase cascade that results in the activation of nitrogen-fixation genes in *Rhizobium meliloti*, and activation of tyrosine kinases is critical in signalling triggered by growth factors and ultraviolet light. We show here that genistein, an inhibitor of protein tyrosine kinase, blocks VEGF induction. Hypoxia increases the kinase activity of pp60c-src and its phosphorylation on tyrosine 416 but does not activate Fyn or Yes. Expression of either a dominant-negative mutant form of c-Src or of Raf-1 markedly reduces VEGF induction. VEGF induction by hypoxia in c-src(-) cells is impaired, although there is a compensatory activation of Fyn. Our results provide an insight into hypoxia-triggered intracellular signalling, define VEGF as a new downstream target for c-SRC, and suggest a role for c-SRC in promoting angiogenesis

All-trans and 9-cis retinoic acid enhance 1,25-dihydroxyvitamin D3-induced monocytic differentiation of U937 cells.

Nakajima H, Kizaki M, Ueno H, et al.

Leuk Res. 1996 Aug; 20(8):665-76.

Retinoic acid (RA) and 1,25-dihydroxyvitamin D3 (D3) are well known for inducing differentiation in many leukemic cell lines. The nuclear signalling pathways of RA and D3 are mediated through their cognate receptors, the retinoic acid receptor (RAR) and vitamin D3 receptor (VDR), respectively. Retinoid X receptor (RXR) is an auxiliary factor that forms a heterodimer with RAR and VDR, enabling their efficient transcriptional activation. 9-cis RA, a high-affinity ligand for RXR, greatly enhanced D3-induced CD14 expression in U937 cells, while RA alone did not induce CD14 expression. 9-cis RA also resulted in morphological changes of U937 cells to macrophage-like cells when combined with D3, while RA alone resulted in granulocyte-like cells. RA and D3 together enhanced c-fms expression, phagocytic activity, and acted synergistically to promote nitroblue tetrazolium reduction activity and inhibit proliferation. Northern analysis showed that U937 cells constitutively expressed RAR-alpha, VDR and RXR-alpha mRNAs. RA or D3 alone or in combination did not affect RAR-alpha and VDR expression, while 9-cis RA and 9-cis RA plus all-trans RA significantly reduced RXR-alpha expression. Interestingly, D3 could restore the down-regulation of RXR-alpha mRNA by 9-cis RA. These findings suggest that there is crossover of the nuclear signalling pathways of RA and D3. This may have clinical implications in that RA and D3 may be used in combination for differentiation-inducing therapy in acute myelogenous leukemia and myelodysplastic syndrome

Resveratrol is a potent inducer of apoptosis in human melanoma cells.

Niles RM, McFarland M, Weimer MB, et al.

Cancer Lett. 2003 Feb 20; 190(2):157-63.

Resveratrol is a plant polyphenol found in grapes and red wine. It has been found to have beneficial effects on the cardiovascular system. Resveratrol also inhibits the growth of various tumor cell lines in vitro and inhibits carcinogenesis in vivo. In this study we examined the effect of resveratrol on growth of two human melanoma cell lines. We found that this plant polyphenol inhibited growth and induced apoptosis in both cell lines, with the amelanotic cell line A375 being more sensitive. The potential involvement of different MAP kinases in the action of resveratrol was also examined. Although resveratrol did not alter the phosphorylation of p38 or JNK MAP kinases in either cell line, it induced phosphorylation of ERK1/2 in A375, but not in SK-mel28 cells. These results suggest that in vivo studies of the effect of resveratrol on melanoma are warranted and that this plant polyphenol might have effectiveness as either a therapeutic or chemopreventive agent against melanoma

[All-trans retinoic acid (Tretinoin)].

Ohno R.

Gan To Kagaku Ryoho. 1997 Apr; 24(6):741-6.

Differentiation therapy with all-trans retinoic acid (ATRA, tretinoin) alone or in combination with chemotherapy induces around 90% complete remission in acute promyelocytic leukemia (APL). By giving non-cross resistant chemotherapy as postremission therapy, more than 50% of APL, especially more than 70% of APL patients of age less than 30, became curable. Since this active form of Vitamin A causes less toxicity and fewer complications compared with other cytotoxic drugs, the medical costs required are less. Therefore, ATRA therapy should be incorporated as a first-line therapy for APL

Induction of apoptosis by garcinol and curcumin through cytochrome c release and activation of caspases in human leukemia HL-60 cells.

Pan MH, Chang WL, Lin-Shiau SY, et al.

J Agric Food Chem. 2001 Mar; 49(3):1464-74.

Garcinol, a polyisoprenylated benzophenone, was purified from *Garcinia indica* fruit rind. The effects of garcinol and curcumin on cell viability in human leukemia HL-60 cells were investigated. Garcinol and curcumin displayed strong growth inhibitory effects against human leukemia HL-60 cells, with estimated IC(50) values of 9.42 and 19.5 microM, respectively. Garcinol was able to induce apoptosis in a concentration- and time-dependent manner; however, curcumin was less effective. Treatment with garcinol caused induction of caspase-3/CPP32 activity in a dose- and time-dependent manner, but not caspase-1 activity, and induced the degradation of poly(ADP-ribose) polymerase (PARP). Pretreatment with caspase-3 inhibitor inhibited garcinol-induced DNA fragmentation. Treatment with garcinol (20 microM) caused a rapid loss of mitochondrial transmembrane potential, release of mitochondrial cytochrome c into cytosol, and subsequent induction of procaspase-9 processing. The cleavage of D4-GDI, an abundant hematopoietic cell GDP dissociation inhibitor for the Ras-related Rho family GTPases, occurred simultaneously with the activation of caspase-3 but preceded DNA fragmentation and the morphological changes associated with apoptotic cell death. Of these, Bcl-2, Bad, and Bax were studied. The level of expression of Bcl-2 slightly decreased, while the levels of Bad and Bax were dramatically increased in cells treated with garcinol. These results indicate that garcinol allows caspase-activated deoxyribonuclease to enter the nucleus and degrade chromosomal DNA and induces DFF-45 (DNA fragmentation factor) degradation. It is suggested that garcinol-induced apoptosis is triggered by the release of cytochrome c into the cytosol, procaspase-9 processing, activation of caspase-3 and caspase-2, degradation of PARP, and DNA fragmentation caused by the caspase-activated deoxyribonuclease through the digestion of DFF-45. The induction of apoptosis by garcinol may provide a pivotal mechanism for its cancer chemopreventive action

Devour Disease with Shark Liver Oil.

Pugliese PT.

1999;

Some biological actions of alkylglycerols from shark liver oil.

Pugliese PT, Jordan K, Cederberg H, et al.

J Altern Complement Med. 1998; 4(1):87-99.

Shark liver oil has been used for over 40 years as both a therapeutic and preventive agent. The active ingredients in shark liver oil have been found to be a group of ether-linked glycerols known as alkylglycerols. Initial clinical use was for treating leukemias, and later to prevent radiation sickness from cancer x-ray therapy. Studies over the last 30 years have shown that alkylglycerols are multifunctional. The level of natural alkylglycerols rises within tumor cells, apparently in an effort to control cell growth. Recent studies indicate that the activation of protein kinase C, an essential step in cell proliferation, can be inhibited by alkylglycerols. This action suggests a competitive inhibition of 1,2-diacylglycerol by alkylglycerols. Further studies on the immunostimulatory action of alkylglycerols suggest a primary action on the macrophage. The process of macrophage activation has been demonstrated with both synthetic and natural alkylglycerols. While the exact mechanism has not been found, both an autocrine and paracrine system have been suggested. Shark liver is a major natural source of alkylglycerols, which have no known side effects in dosages of 100 mg three times a day. The information presented in this article suggests that alkylglycerols may be used both as an adjunct therapy in the treatment of neoplastic disorders and as an immune booster in infectious diseases

Modulation in vitro of human natural cytotoxicity, lymphocyte proliferative response to mitogens and cytokine production by

essential fatty acids.

Purasiri P, Mckechnie A, Heys SD, et al.

Immunology. 1997 Oct; 92(2):166-72.

Essential fatty acids (EFA) have been shown in animal studies to have a differential effect on various aspects of immune reactivity. However, there have been few studies in humans. Therefore, we elected to investigate the effects of a variety of EFA [gamma-linolenic acid (GLA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] in vitro on human blood lymphocyte reactivity, cytokine secretion and natural cytotoxicity. The proliferative response to polyclonal mitogens (phytohaemagglutinin, pokeweed mitogen, concanavalin A), as measured by [3H]thymidine incorporation into newly synthesized lymphocytes, was inhibited ($P < 0.05$) by all EFAs tested, in a dose-dependent manner (3-15 micrograms/ml). The greatest inhibition of proliferation was caused by EPA and DHA. Similarly, EPA, DHA and GLA significantly reduced cytotoxic activity [expressed as lytic units, using 51 chromium-release assays natural killer (NK) (K562 cells) and lymphokine-activated (LAK) (Daudi cells) cells] ($P < 0.05$) in a concentration-dependent manner (5-50 micrograms/ml), without affecting cell viability. EPA and DHA exhibited greater suppression than GLA. Furthermore, the inhibition of cell proliferation and suppression of natural cytotoxicity was associated with marked decrease in cytokine [interleukin-1 (IL-1), IL-2, tumour necrosis factor-alpha (TNF-alpha) and interferon-gamma (IFN-gamma)] production in vitro. Our findings demonstrate that EFAs (GLA, EPA, DHA) have the potential to inhibit significantly various aspects of human lymphocyte cell-mediated and humoral immune reactivities

All-trans retinoic acid in hematological malignancies, an update. GER (Gruppo Ematologico Retinoidi).

Sacchi S, Russo D, Avvisati G, et al.

Haematologica. 1997 Jan; 82(1):106-21.

BACKGROUND AND OBJECTIVE: During the past ten years, the study of retinoids has undergone a total transformation. The Italian Society of Experimental Hematology decided to discuss these advances at a meeting in Florence on April 18, 1996. **INFORMATION SOURCES:** The material examined in the present review includes articles and abstracts published in journals covered by the Science Citation Index and Medline. In addition, all the authors of the present article have been actively working in the field of retinoids and have contributed several papers. Summaries of their oral presentations at the Florence meeting are reported in the Appendix to this review article. **STATE OF ART AND PERSPECTIVES:** One of the most important advances has been the elucidation of new molecular mechanisms of control of gene expression by retinoids. A number of new retinoids have been synthesized by chemists, some of which are being screened for potential clinical use, and a few have already had a tremendous impact on clinical practice. The most important achievements have been obtained in acute promyelocytic leukemia. In 1988 a Chinese group working in Shanghai showed that using all-trans retinoic acid (ATRA) alone 94% of acute promyelocytic leukemic patients obtained complete remission through differentiation of the leukemic clone. This result transformed a dream into reality and allowed researchers to move from laboratory experience to clinical applications of this differentiating therapy. Expanding the spectrum of hematological malignancies that may respond to ATRA remains a challenge; however, several results show some activity of retinoids alone or in combination with other drugs in juvenile chronic myeloid leukemia (CML), myelodysplastic syndrome, cutaneous T-cell lymphoma and CML. Particularly interesting are the studies that explored the potential clinical synergism of ATRA-based combination therapies with growth factors, other differentiating agents such as vitamin D3, immunomodulators like interferons, or chemotherapeutic agents, in particular Ara-C, all of which show promising in vitro effects when used in combination with retinoids

Simultaneous elevation in the serum concentrations of the angiogenic growth factors VEGF and bFGF is an independent predictor of poor prognosis in non-Hodgkin lymphoma: a single-institution study of 200 patients.

Salven P, Orpana A, Teerenhovi L, et al.

Blood. 2000 Dec 1; 96(12):3712-8.

High serum concentrations of vascular endothelial growth factor (S-VEGF) and basic fibroblast growth factor (S-bFGF) are associated with unfavorable clinical characteristics in cancer. The combined effect of S-VEGF and S-bFGF on the survival of 200 patients with non-Hodgkin lymphoma (NHL) was studied. High S-VEGF and S-bFGF at diagnosis were associated with poor survival with the medians, the highest tertiles, or the highest quartiles as the cutoff values. The highest prognostic power was obtained when S-VEGF and S-bFGF were examined as a combination. Patients who had both S-VEGF and S-bFGF within the highest quartiles had only a 21% 5-year survival rate in contrast to a 64% 5-year survival rate among patients with both factors within the 3 lowest quartiles ($P < .0001$). Simultaneous elevation of S-VEGF and S-bFGF was associated with poor survival in different grades of lymphomas and in the largest histologic subgroup, the large-cell diffuse and immunoblastic lymphomas. S-VEGF (relative risk [RR], 1.83; $P = .019$) and S-bFGF (RR, 2.02; $P = .0049$) had independent influences on survival in multivariate models when tested together with the components of the International Prognostic Index (IPI). Patients with both S-

VEGF and S-bFGF within the highest quartiles had nearly 3 times higher risk for death (RR, 2.90; 95% confidence interval [CI], 1.56-5.40; P = ".0008") than the rest of the patients. This RR was higher than the relative risks associated with any of the components of the IPI in the same model. The authors conclude that the combination of S-VEGF and S-bFGF is a powerful prognostic variable in NHL. (Blood. 2000;96:3712-3718)

Regulation of cellular thiols in human lymphocytes by alpha-lipoic acid: a flow cytometric analysis.

Sen CK, Roy S, Han D, et al.

Free Radic Biol Med. 1997; 22(7):1241-57.

Modulation of cellular thiols is an effective therapeutic strategy, particularly in the treatment of AIDS. Lipoic acid, a metabolic antioxidant, functions as a redox modulator and has proven clinically beneficial effects. It is also used as a dietary supplement. We utilized the specific capabilities of N-ethylmaleimide to block total cellular thiols, phenylarsine oxide to block vicinal dithiols, and buthionine sulfoximine to deplete cellular GSH to flow cytometrically investigate how these thiol pools are influenced by exogenous lipoate treatment. Low concentrations of lipoate and its analogue lipoamide increased Jurkat cell GSH in a dose-dependent manner between 10 (25 microM for lipoamide) to 100 microM. This was also observed in mitogenically stimulated peripheral blood lymphocytes (PBL). Studies with Jurkat cells and its Wurzburg subclone showed that lipoate dependent increase in cellular GSH was similar in CD4+ and - cells. Chronic (16 week) exposure of cells to lipoate resulted in further increase of total cellular thiols, vicinal dithiols, and GSH. High concentration (2 and 5 mM) of lipoate exhibited cell shrinkage, thiol depletion, and DNA fragmentation effects. Based on similar effects of octanoic acid, the cytotoxic effects of lipoate at high concentration could be attributed to its fatty acid structure. In certain diseases such as AIDS and cancer, elevated plasma glutamate lowers cellular GSH by inhibiting cystine uptake. Low concentrations of lipoate and lipoamide were able to bypass the adverse effect of elevated extracellular glutamate. A heterogeneity in the thiol status of PBL was observed. Lipoate, lipoamide, or N-acetylcysteine corrected the deficient thiol status of cell subpopulations. Hence, the favorable effects of low concentrations of lipoate treatment appears clinically relevant

Fas mediated apoptosis of human Jurkat T-cells: intracellular events and potentiation by redox-active alpha-lipoic acid.

Sen CK, Sashwati R, Packer L.

Cell Death Differ. 1999 May; 6(5):481-91.

Activation of caspases is required in Fas receptor mediated apoptosis. Maintenance of a reducing environment inside the cell has been suggested to be necessary for caspase activity during apoptosis. We explored the possibility to potentiate Fas mediated killing of tumor cells by alpha-lipoic acid (LA), a redox-active drug and nutrient that is intracellularly reduced to a potent reductant dihydrolipoic acid. Treatment of cells with 100 microM LA for 72 h markedly potentiated Fas-mediated apoptosis of leukemic Jurkat cells but not that of peripheral blood lymphocytes from healthy humans. In Jurkat, Fas activation was followed by rapid loss of cell thiols, decreased mitochondrial membrane potential, increased [Ca²⁺]_i and increased PKC activity; all these responses were potentiated in LA pretreated cells. PKCdelta played an important role in mediating the effect of LA on Fas-mediated cell death. In response to Fas activation LA treatment potentiated caspase 3 activation by over 100%. The ability of LA to potentiate Fas mediated killing of leukemic cells was abrogated by a caspase 3 inhibitor suggesting that increased caspase 3 activity in LA-treated Fas-activated cells played an important role in potentiating cell death. This work provides first evidence showing that inducible caspase 3 activity may be pharmacologically up-regulated by reducing agents such as dihydrolipoic acid

Hepatocyte growth factor (HGF) protects c-met-expressing Burkitt's lymphoma cell lines from apoptotic death induced by DNA damaging agents.

Skibinski G, Skibinska A, James K.

Eur J Cancer. 2001 Aug; 37(12):1562-9.

The relative sensitivity of neoplastic cells to DNA damaging agents is a key factor in cancer therapy. In this paper, we show that pretreatment of Burkitt's lymphoma cell lines expressing the c-met protooncogene with hepatocyte growth factor (HGF) protects them from death induced by DNA damaging agents commonly used in tumour therapy. This protection was observed in assays based on morphological assessment of apoptotic cells and DNA fragmentation assays. The protection was dose- and time-dependent -- maximal protection requiring pre-incubation with 100 ng/ml HGF for 48 h. Western blotting analysis and flow cytometric studies revealed that HGF inhibited doxorubicin- and etoposide-induced decreases in the levels of the anti-apoptotic proteins Bcl-X(L), and to a lesser extent Bcl-2, without inducing changes in the pro-apoptotic Bax protein. Overall, these studies suggest that the accumulation of HGF within the microenvironment of neoplastic cells may contribute to the development of a chemoresistant phenotype

Induction of the differentiation of HL-60 promyelocytic leukemia cells by vitamin E and other antioxidants in combination with low levels of vitamin D3: possible relationship to NF-kappaB.

Sokoloski JA, Hodnick WF, Mayne ST, et al.

Leukemia. 1997 Sep; 11(9):1546-53.

Epidemiological studies have provided evidence that diets rich in antioxidant nutrients may reduce the risk of cancer. To evaluate the possibility that dietary phytochemicals with antioxidant potential would create an environment capable of affecting the differentiation of HL-60 leukemia cells, we measured the effects of vitamin E and other dietary antioxidants on the differentiation produced by low levels of vitamin D3 and analogs thereof. Vitamin E succinate and other antioxidant compounds (ie butylated hydroxyanisole, beta-carotene and lipoic acid) used alone had no significant effect on the differentiation of HL-60 cells; however, these agents markedly increased the differentiation produced by vitamin D3. Previous studies from this laboratory have shown that a sequence-specific antisense phosphorothioate oligonucleotide to the Rel A subunit of NF-kappaB enhanced the differentiation of HL-60 cells produced by several inducing agents. Consistent with these observations, vitamin E succinate caused a marked reduction in the nuclear content of NF-kappaB both in the presence and absence of vitamin D3. These findings suggest that NF-kappaB may be a factor in regulating the differentiation of myeloid leukemia cells. The results also indicate that combinations of vitamin D3 and analogs thereof with dietary antioxidants may be useful in overcoming the differentiation block present in acute promyelocytic leukemia cells

Complete remission following recombinant interferon alpha-2a in a patient with diffuse large B cell cutaneous lymphoma.

Tourani JM, Leaute JB, Lessana-Leibowitch M, et al.

Nouv Rev Fr Hematol. 1989; 31(4):315-6.

Recombinant interferon alpha (r IFN alpha) has shown significant antitumor activity in patients with follicular small cleaved cell (low-grade non-Hodgkin's lymphomas) and cutaneous T-cell lymphomas. However, IFN alpha seems to be less effective in patients with intermediate or high-grade lymphomas. This case report describes a patient with an initial diagnosis of low grade B-cell lymphoma with histologic conversion to diffuse large B-cell (B1+, Kappa+) cutaneous lymphoma. This tumor proved refractory to chemotherapy but a complete and durable remission was induced with R IFN alpha 2a treatment

Differentiation-promoting effect of 1-O (2 methoxy) hexadecyl glycerol in human colon cancer cells.

Wang H, Rajagopal S, Reynolds S, et al.

J Cell Physiol. 1999 Feb; 178(2):173-8.

Alkylglycerols are naturally occurring bioactive ether lipids found in great abundance in the livers of many marine species. In this study, we evaluated the differentiation-promoting potential of a methoxy substituted alkylglycerol--1-O (2 methoxy) hexadecyl glycerol (MHG)--to promote a more benign or differentiated phenotype in human colon cancer cells. Three cell lines with different biological and phenotypic properties were used. They were the moderately differentiated and growth factor-responsive Moser, the growth factor-unresponsive and malignant HT29, and the poorly differentiated and growth factor-unresponsive HCT116. Treatment of these cell lines with MHG resulted in a downmodulation of cellular proliferation, a reduced propensity for anchorage-independent growth, and a reduced capacity in cellular invasion. Induction of the colon-associated and differentiation-related molecule carcinoembryonic antigen was also observed in the three cell lines. Induction of the transformation-sensitive and differentiation-related glycoprotein fibronectin was observed in the HT29 cells. It is concluded that MHG was biologically active and promoted a more benign or differentiated phenotype in these colon cancer cells. Since differentiation-inducing agents may possess chemoprevention properties, the use of MHG and the alkylglycerols in inducing differentiation or in chemoprevention of malignant diseases warrants further investigation

Cerivastatin triggers tumor-specific apoptosis with higher efficacy than lovastatin.

Wong WW, Tan MM, Xia Z, et al.

Clin Cancer Res. 2001 Jul; 7(7):2067-75.

The statin family of drugs inhibits 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, the rate-limiting enzyme of the mevalonate pathway, and is used clinically as a safe and effective approach in the control of hypercholesterolemia. We have shown previously (Dimitroulakos, J., Nohynek, D., Backway, K. L., Hedley, D. W., Yeger, H., Freedman, M. H., Minden, M D.,

and Penn, L. Z. Increased sensitivity of acute myelogenous leukemias to lovastatin-induced apoptosis: a potential therapeutic approach. *Blood*, 93: 1308-1318, 1999) that lovastatin, a prototypic member of the statin family, can induce apoptosis of human acute myeloid leukemia (AML) cells in a sensitive and specific manner. In the present study, we evaluated the relative potency and mechanism of action of the newer synthetic statins, fluvastatin, atorvastatin, and cerivastatin, to trigger tumor-specific apoptosis. Cerivastatin is at least 10 times more potent than the other statins at inducing apoptosis in AML cell lines. Cerivastatin-induced apoptosis is reversible with the addition of the immediate product of the HMG-CoA reductase reaction, mevalonate, or with a distal product of the pathway, geranylgeranyl pyrophosphate. This suggests protein geranylgeranylation is an essential downstream component of the mevalonate pathway for cerivastatin similar to lovastatin-induced apoptosis. The enhanced potency of cerivastatin expands the number of AML patient samples as well as the types of malignancies, which respond to statin-induced apoptosis with acute sensitivity. Cells derived from acute lymphocytic leukemia are only weakly sensitive to lovastatin cytotoxicity but show robust response to cerivastatin. Importantly, cerivastatin is not cytotoxic to nontransformed human bone marrow progenitors. These results strongly support the further testing of cerivastatin as a novel anticancer therapeutic alone and in combination with other agents in vivo

Curcumin inhibits IL1 alpha and TNF-alpha induction of AP-1 and NF-kB DNA-binding activity in bone marrow stromal cells.

Xu YX, Pindolia KR, Janakiraman N, et al.

Hematopathol Mol Hematol. 1997; 11(1):49-62.

We have previously demonstrated that anti-inflammatory and antioxidant compound curcumin (diferuloyl-methane) inhibits the expression of monocyte chemoattractant protein-1 (MCP-1/JE) in bone marrow stromal cells by suppressing the transcriptional activity of the MCP-1/JE gene. Since both AP-1 (TRE) and NF-kB (kB) binding motifs are present in the promoter of MCP-1/JE gene, we examined the effect of curcumin on IL1 alpha- and TNF-alpha-induced activation of ubiquitous transcription factors AP-1 and NF-kB by electrophoretic mobility shift assay and Western blotting. IL1 alpha and TNF-alpha rapidly induced both AP-1 and NF-kB DNA binding activities in +/(-)1.LDA11 stromal cells. However, treatment of these cells with curcumin blocked the activation of AP-1 and NF-kB by both cytokines. These data suggest that inhibition of MCP-1/JE transcription by curcumin involves blocking of AP-1 and NF-kB activation by IL1 alpha or TNF-alpha

All-trans retinoic acid combined with interferon-alpha effectively inhibits granulocyte-macrophage colony formation in chronic myeloid leukemia.

Zheng A, Savolainen ER, Koistinen P.

Leuk Res. 1996 Mar; 20(3):243-8.

We investigated the effect of all-trans retinoic acid (ATRA) alone and in combination with interferon-alpha (IFN-alpha) on the granulocyte-macrophage (GM) colony formation of peripheral blood progenitors isolated from patients with chronic myeloid leukemia (CML) (n = 12) or other myeloproliferative disorders (n = 10) as well as from healthy controls (n = 7). The ATRA or IFN-alpha alone inhibited slightly, but not significantly, the GM colony growth in CML. Granulocyte-macrophage colony formation decreased significantly (P<0.05) when ATRA and IFN-alpha were combined (114 +/- 96 versus 74 +/- 53 colonies/10(4) mononuclear cells). The combination did not have any inhibitory effect on the other MPDs. In healthy controls, ATRA or IFN-alpha alone or their combination stimulated GM colony growth, the increase being from 22 +/- 9 to 39 +/- 16 colonies for ATRA (P<0.05), up to 47 +/- 12 colonies for IFN-alpha (P<0.05) and up to 50 +/- 19 colonies for the combination (P<0.05). In conclusion, ATRA combined with IFN-alpha inhibits GM colony growth in CML. This combination may be worth testing clinically as a treatment of CML

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