

LE Magazine May 2007

Journal
ABSTRACTS**Pomegranate****POMEGRANATE JUICE PROTECTS NITRIC OXIDE AGAINST OXIDATIVE DESTRUCTION AND ENHANCES THE BIOLOGICAL ACTIONS OF NITRIC OXIDE.**

Pomegranate juice (PJ), which is a rich source of potent flavonoid antioxidants, was tested for its capacity to protect nitric oxide (NO) against oxidative destruction and enhance the biological actions of NO. Employing chemiluminescence headspace analysis, PJ was found to be a potent inhibitor of superoxide anion-mediated disappearance of NO. PJ was much more potent than Concord grape juice, blueberry juice, red wine, ascorbic acid, and DL-alpha-tocopherol. As little as 3 microl of a 6-fold dilution of PJ, in a reaction volume of 5000 microl, produced a marked antioxidant effect, whereas 300 microl of undiluted blueberry juice or nearly 1000 microl of undiluted Concord grape juice were required to produce similar effects. PJ and other antioxidant-containing products were found to augment the anti-proliferative action of NO (DETA/NO) on vascular smooth muscle cell (rat aorta) proliferation. PJ was much more effective than the other products tested and elicited no effects when tested alone in the absence of added NO. Similarly, neither PJ nor the other products enhanced the anti-proliferative action of alpha-difluoromethylornithine, a stable substance that inhibits cell growth by NO-independent mechanisms. In order to determine whether PJ is capable of increasing the production of NO by vascular endothelial cells, PJ was tested for its capacity to upregulate and/or activate endothelial NO synthase (eNOS) in bovine pulmonary artery endothelial cells. PJ elicited no effects on eNOS protein expression or catalytic activity. Moreover, PJ did not enhance promoter activity in the eNOS gene (COS-7 cells transfected with eNOS). These observations indicate that PJ possesses potent antioxidant activity that results in marked protection of NO against oxidative destruction, thereby resulting in augmentation of the biological actions of NO.

Nitric Oxide. 2006 Sep;15(2):93-102

REACTIVE OXYGEN SPECIES AND VASCULAR REMODELLING IN HYPERTENSION: STILL ALIVE.

Reactive oxygen species (ROS) are reactive derivatives of O₂ metabolism, including superoxide anion, hydrogen peroxide, hydroxyl radical and nitric oxide. All types of vascular cells produce ROS, primarily via cell membrane-associated NAD(P)H oxidase. Cardiovascular diseases, such as hypertension, are associated with increased ROS formation (oxidative stress). Oxidative excess in the vasculature reduces levels of the vasodilator nitric oxide, causes tissue injury, promotes protein oxidation and DNA damage, and induces proinflammatory responses. ROS are also important intracellular signalling molecules that regulate vascular function by modulating vascular cell contraction/dilation, migration, growth/apoptosis, and extracellular matrix protein turnover, which contribute to vascular remodelling. Interventions to decrease ROS bioavailability regress remodelling and reduce blood pressure in experimental hypertension. Such strategies may have therapeutic potential in cardiovascular diseases.

Can J Cardiol. 2006 Sep;22(11):947-51

POMEGRANATE JUICE REDUCES OXIDIZED LOW-DENSITY LIPOPROTEIN DOWNREGULATION OF ENDOTHELIAL NITRIC OXIDE SYNTHASE IN HUMAN CORONARY ENDOTHELIAL CELLS.

We examined the hypothesis that pomegranate juice (PJ) can revert the potent downregulation of the expression of endothelial nitric-oxide synthase (NOSIII) induced by oxidized low-density lipoprotein (oxLDL) in human coronary endothelial cells. Western blot and Northern blot analyses showed a significant decrease of NOSIII expression after a 24-h treatment with oxLDL. Accordingly, we observed a significant dose-dependent reduction in nitric oxide bioactivity represented by both basal and bradykinin-stimulated cellular cGMP accumulation. These phenomena were corrected significantly by the concomitant treatment with PJ. Our data suggest that PJ can exert beneficial effects on the evolution of clinical vascular complications, coronary heart disease, and atherogenesis in humans by enhancing the NOSIII bioactivity.

Nitric Oxide. 2006 Nov;15(3):259-63

EFFECTS OF A POMEGRANATE FRUIT EXTRACT RICH IN PUNICALAGIN ON OXIDATION-SENSITIVE GENES AND

BACKGROUND: Atherosclerosis is enhanced in arterial segments exposed to disturbed flow. Perturbed shear stress increases the expression of oxidation-sensitive responsive genes (such as ELK-1 and p-CREB). Polyphenolic antioxidants contained in the juice derived from the pomegranate contribute to the reduction of oxidative stress and atherogenesis during disturbed shear stress. **AIM OF THE STUDY:** To evaluate the effects of intervention with the Pomegranate Fruit Extract (PFE) rich in polyphenols (punicalagin, which is a potent antioxidant) on ELK-1, p-CREB, and endothelial nitric oxide synthase (eNOS) expression induced by high shear stress *in vitro* and *in vivo*. **RESULTS:** At the doses used in the study, both the PFE and the regular pomegranate juice concentrate reduced the activation of ELK-1 and p-CREB and increased eNOS expression (which was decreased by perturbed shear stress) in cultured human endothelial cells and in atherosclerosis-prone areas of hypercholesterolemic mice. PFE and pomegranate juice increased cyclic GMP levels while there was no significant effect of both compounds on the conversion of L-arginine to L-citrulline. Administration of these compounds to hypercholesterolemic mice significantly reduced the progression of atherosclerosis and isoprostane levels and increased nitrates. This protective effect was relevant with PFE. Vasomotor reactivity was improved and EC(25) values in response to Ach and NONOate were significantly increased in treated mice in comparison to controls. **CONCLUSION:** This study indicates that the proatherogenic effects induced by perturbed shear stress can be also reversed by chronic administration of PFE.

Cardiovasc Res. 2007 Jan 15;73(2):414-23

POMEGRANATE JUICE SUGAR FRACTION REDUCES MACROPHAGE OXIDATIVE STATE, WHEREAS WHITE GRAPE JUICE SUGAR FRACTION INCREASES IT.

The antiatherogenic properties of pomegranate juice (PJ) were attributed to its antioxidant potency and to its capacity to decrease macrophage oxidative stress, the hallmark of early atherogenesis. PJ polyphenols and sugar-containing polyphenolic anthocyanins were shown to confer PJ its antioxidant capacity. In the present study, we questioned whether PJ simple or complex sugars contribute to the antioxidative properties of PJ in comparison to white grape juice (WGJ) sugars. Whole PJ decreased cellular peroxide levels in J774A.1 macrophage cell-line by 23% more than PJ polyphenol fraction alone. Thus, we next determined the contribution of the PJ sugar fraction to the decrease in macrophage oxidative state. Increasing concentrations of the PJ sugar fraction resulted in a dose-dependent decrement in macrophage peroxide levels, up to 72%, compared to control cells. On the contrary, incubation of the cells with WGJ sugar fraction at the same concentrations resulted in a dose-dependent increment in peroxide levels by up to 37%. The two sugar fractions from PJ and from WGJ showed opposite effects (antioxidant for PJ and pro-oxidant for WGJ) also in mouse peritoneal macrophages (MPM) from control as well as from streptozotocin-induced diabetic Balb/C mice. PJ sugar consumption by diabetic mice for 10 days resulted in a small but significant decrement in their peritoneal macrophage total peroxide levels and an increment in cellular glutathione content, compared to MPM harvested from control diabetic mice administrated with water. In contrast, WGJ sugar consumption by diabetic mice resulted in a 22% increment in macrophage total peroxide levels and a 45% decrement in cellular glutathione content. Paraonase 2 activity in macrophages increases under oxidative stress conditions. Indeed, macrophage paraonase 2 activity was decreased after PJ sugars supplementation, but increased after WGJ sugars supplementation. We conclude that PJ sugar fraction, unlike WGJ sugar fraction, decreases macrophage oxidative state under normal and under diabetic conditions. These antioxidant/antiatherogenic effects could be due to the presence of unique complex sugars and/or phenolic sugars in PJ.

Atherosclerosis. 2006 Sep;188(1):68-76

ANTI-OXIDATIVE EFFECTS OF POMEGRANATE JUICE (PJ) CONSUMPTION BY DIABETIC PATIENTS ON SERUM AND ON MACROPHAGES.

Diabetes is associated with increased oxidative stress and atherosclerosis development. In the present study, we investigated the effects of pomegranate juice (PJ; which contains sugars and potent anti-oxidants) consumption by diabetic patients on blood diabetic parameters, and on oxidative stress in their serum and macrophages. Ten healthy subjects (controls) and 10 non-insulin dependent diabetes mellitus (NIDDM) patients who consumed PJ (50ml per day for 3 months) participated in the study. In the patients versus controls serum levels of lipid peroxides and thiobarbituric acid reactive substances (TBARS) were both increased, by 350% and 51%, respectively, whereas serum SH groups content and paraonase 1 (PON1) activity, were both decreased (by 23%). PJ consumption did not affect serum glucose, cholesterol and triglyceride levels, but it resulted in a significant reduction in serum lipid peroxides and TBARS levels by 56% and 28%, whereas serum SH groups and PON1 activity significantly increased by 12% and 24%, respectively. In the patients versus controls monocytes-derived macrophages (HMDM), we observed increased level of cellular peroxides (by 36%), and decreased glutathione content (by 64%). PJ consumption significantly reduced cellular peroxides (by 71%), and increased glutathione levels (by 141%) in the patients' HMDM. The patients' versus control HMDM took up oxidized LDL (Ox-LDL) at enhanced rate (by 37%) and PJ consumption significantly decreased the extent of Ox-LDL cellular uptake (by 39%). We thus conclude that PJ consumption by diabetic patients did not worsen the diabetic parameters, but rather resulted in anti-oxidative effects on serum and macrophages, which could contribute to attenuation of atherosclerosis development in these patients.

POMEGRANATE (PUNICA GRANATUM) PURE CHEMICALS SHOW POSSIBLE SYNERGISTIC INHIBITION OF HUMAN PC-3 PROSTATE CANCER CELL INVASION ACROSS MATRIGEL.

Four pure chemicals, ellagic acid (E), caffeic acid (C), luteolin (L) and punicalic acid (P), all important components of the aqueous compartments or oily compartment of pomegranate fruit (*Punica granatum*), and each belonging to different representative chemical classes and showing known anticancer activities, were tested as potential inhibitors of in vitro invasion of human PC-3 prostate cancer cells in an assay employing Matrigel artificial membranes. All compounds significantly inhibited invasion when employed individually. When C, P, and L were equally combined at the same gross dosage (4 microg/ml) as when the compounds were tested individually, a supraditive inhibition of invasion was observed, measured by the Kruskal-Wallis non-parametric test.

Invest New Drugs. 2005 Mar;23(2):121-2

IN VITRO ANTIPROLIFERATIVE, APOPTOTIC AND ANTIOXIDANT ACTIVITIES OF PUNICALAGIN, ELLAGIC ACID AND A TOTAL POMEGRANATE TANNIN EXTRACT ARE ENHANCED IN COMBINATION WITH OTHER POLYPHENOLS AS FOUND IN POMEGRANATE JUICE.

Pomegranate (*Punica granatum* L.) fruits are widely consumed as juice (PJ). The potent antioxidant and anti-atherosclerotic activities of PJ are attributed to its polyphenols including punicalagin, the major fruit ellagitannin, and ellagic acid (EA). Punicalagin is the major antioxidant polyphenol ingredient in PJ. Punicalagin, EA, a standardized total pomegranate tannin (TPT) extract and PJ were evaluated for in vitro antiproliferative, apoptotic and antioxidant activities. Punicalagin, EA and TPT were evaluated for antiproliferative activity at 12.5-100 microg/ml on human oral (KB, CAL27), colon (HT-29, HCT116, SW480, SW620) and prostate (RWPE-1, 22Rv1) tumor cells. Punicalagin, EA and TPT were evaluated at 100 microg/ml concentrations for apoptotic effects and at 10 microg/ml concentrations for antioxidant properties. However, to evaluate the synergistic and/or additive contributions from other PJ phytochemicals, PJ was tested at concentrations normalized to deliver equivalent amounts of punicalagin (w/w). Apoptotic effects were evaluated against the HT-29 and HCT116 colon cancer cell lines. Antioxidant effects were evaluated using inhibition of lipid peroxidation and Trolox equivalent antioxidant capacity (TEAC) assays. Pomegranate juice showed greatest antiproliferative activity against all cell lines by inhibiting proliferation from 30% to 100%. At 100 microg/ml, PJ, EA, punicalagin and TPT induced apoptosis in HT-29 colon cells. However, in the HCT116 colon cells, EA, punicalagin and TPT but not PJ induced apoptosis. The trend in antioxidant activity was PJ>TPT>punicalagin>EA. The superior bioactivity of PJ compared to its purified polyphenols illustrated the multifactorial effects and chemical synergy of the action of multiple compounds compared to single purified active ingredients.

J Nutr Biochem. 2005 Jun;16(6):360-7

POMEGRANATE FRUIT JUICE FOR CHEMOPREVENTION AND CHEMOTHERAPY OF PROSTATE CANCER.

Prostate cancer is the most common invasive malignancy and the second leading cause of cancer-related deaths among U.S. males, with a similar trend in many Western countries. One approach to control this malignancy is its prevention through the use of agents present in diet consumed by humans. Pomegranate from the tree *Punica granatum* possesses strong antioxidant and antiinflammatory properties. We recently showed that pomegranate fruit extract (PFE) possesses remarkable antitumor-promoting effects in mouse skin. In this study, employing human prostate cancer cells, we evaluated the antiproliferative and proapoptotic properties of PFE. PFE (10-100 microg/ml; 48 h) treatment of highly aggressive human prostate cancer PC3 cells resulted in a dose-dependent inhibition of cell growth/cell viability and induction of apoptosis. Immunoblot analysis revealed that PFE treatment of PC3 cells resulted in (i) induction of Bax and Bak (proapoptotic); (ii) down-regulation of Bcl-X(L) and Bcl-2 (antiapoptotic); (iii) induction of WAF1/p21 and KIP1/p27; (iv) a decrease in cyclins D1, D2, and E; and (v) a decrease in cyclin-dependent kinase (cdk) 2, cdk4, and cdk6 expression. These data establish the involvement of the cyclin kinase inhibitor-cyclin-cdk network during the antiproliferative effects of PFE. Oral administration of PFE (0.1% and 0.2%, wt/vol) to athymic nude mice implanted with androgen-sensitive CWR22Rnu1 cells resulted in a significant inhibition in tumor growth concomitant with a significant decrease in serum prostate-specific antigen levels. We suggest that pomegranate juice may have cancer-chemopreventive as well as cancer-chemotherapeutic effects against prostate cancer in humans.

Proc Natl Acad Sci U S A. 2005 Oct 11;102(41):14813-8

POMEGRANATE JUICE DECREASES AMYLOID LOAD AND IMPROVES BEHAVIOR IN A MOUSE MODEL OF ALZHEIMER'S DISEASE.

Although there are no proven ways to delay onset or slow progression of Alzheimer's disease (AD), studies suggest that diet can affect risk. Pomegranates contain very high levels of antioxidant polyphenolic substances as compared to other fruits and vegetables. Polyphenols have been shown to be neuroprotective in different model systems. We asked whether dietary

supplementation with pomegranate juice (PJ) would influence behavior and AD-like pathology in a transgenic mouse model. Transgenic mice (APP(sw)/Tg2576) received either PJ or sugar water control from 6 to 12.5 months of age. PJ-treated mice learned water maze tasks more quickly and swam faster than controls. Mice treated with PJ had significantly less (approximately 50%) accumulation of soluble Abeta42 and amyloid deposition in the hippocampus as compared to control mice. These results suggest that further studies to validate and determine the mechanism of these effects, as well as whether substances in PJ may be useful in AD, should be considered.

Neurobiol Dis. 2006 Dec;24(3):506-15

PHOTOCHEMOPREVENTIVE EFFECT OF POMEGRANATE FRUIT EXTRACT ON UVA-MEDIATED ACTIVATION OF CELLULAR PATHWAYS IN NORMAL HUMAN EPIDERMAL KERATINOCYTES.

UVA is the major portion (90-99%) of solar radiation reaching the surface of the earth and has been described to lead to formation of benign and malignant tumors. UVA-mediated cellular damage occurs primarily through the release of reactive oxygen species and is responsible for immunosuppression, photodermatoses, photoaging and photocarcinogenesis. Pomegranate fruit extract (PFE) possesses strong antioxidant and anti-inflammatory properties. Our recent studies have shown that PFE treatment of normal human epidermal keratinocytes (NHEK) inhibits UVB-mediated activation of MAPK and NF-kappaB pathways. Signal transducers and activators of transcription 3 (STAT3), Protein Kinase B/AKT and Map Kinases (MAPKs), which are activated by a variety of factors, modulate cell proliferation, apoptosis and other biological activities. The goal of this study was to determine whether PFE affords protection against UVA-mediated activation of STAT3, AKT and extracellular signal-regulated kinase (ERK1/2). Immunoblot analysis demonstrated that 4 J/cm² of UVA exposure to NHEK led to an increase in phosphorylation of STAT3 at Tyr705, AKT at Ser473 and ERK1/2. Pretreatment of NHEK with PFE (60-100 microg/mL) for 24 h before exposure to UVA resulted in a dose-dependent inhibition of UVA-mediated phosphorylation of STAT3 at Tyr705, AKT at Ser473 and ERK1/2. mTOR, structurally related to PI3K, is involved in the regulation of p70S6K, which in turn phosphorylates the S6 protein of the 40S ribosomal subunit. We found that UVA radiation of NHEK resulted in the phosphorylation of mTOR at Thr2448 and p70S6K at Thr421/Ser424. PFE pretreatment resulted in a dose-dependent inhibition in the phosphorylation of mTOR at Thr2448 and p70S6K at Thr421/Ser424. Our data further demonstrate that PFE pretreatment of NHEK resulted in significant inhibition of UVA exposure-mediated increases in Ki-67 and PCNA. PFE pretreatment of NHEK was found to increase the cell-cycle arrest induced by UVA in the G1 phase of the cell cycle and the expression of Bax and Bad (proapoptotic proteins), with downregulation of Bcl-X(L) expression (antiapoptotic protein). Our data suggest that PFE is an effective agent for ameliorating UVA-mediated damages by modulating cellular pathways and merits further evaluation as a photochemopreventive agent.

Photochem Photobiol. 2006 Mar-Apr;82(2):398-405

POMEGRANATE AS A COSMECEUTICAL SOURCE: POMEGRANATE FRACTIONS PROMOTE PROLIFERATION AND PROCOLLAGEN SYNTHESIS AND INHIBIT MATRIX METALLOPROTEINASE-1 PRODUCTION IN HUMAN SKIN CELLS.

Pomegranate (*Punica granatum*) is an ancient fruit with exceptionally rich ethnomedical applications. The peel (pericarp) is well regarded for its astringent properties; the seeds for conferring invulnerability in combat and stimulating beauty and fertility. Here, aqueous fractions prepared from the fruit's peel and fermented juice and lipophilic fractions prepared from pomegranate seeds were examined for effects on human epidermal keratinocyte and human dermal fibroblast function. Pomegranate seed oil, but not aqueous extracts of fermented juice, peel or seed cake, was shown to stimulate keratinocyte proliferation in monolayer culture. In parallel, a mild thickening of the epidermis (without the loss of ordered differentiation) was observed in skin organ culture. The same pomegranate seed oil that stimulated keratinocyte proliferation was without effect on fibroblast function. In contrast, pomegranate peel extract (and to a lesser extent, both the fermented juice and seed cake extracts) stimulated type I procollagen synthesis and inhibited matrix metalloproteinase-1 (MMP-1; interstitial collagenase) production by dermal fibroblasts, but had no growth-supporting effect on keratinocytes. These results suggest heuristic potential of pomegranate fractions for facilitating skin repair in a polar manner, namely aqueous extracts (especially of pomegranate peel) promoting regeneration of dermis, and pomegranate seed oil promoting regeneration of epidermis.

J Ethnopharmacol. 2006 Feb 20;103(3):311-8

NONCALCEMIC ACTIONS OF VITAMIN D RECEPTOR LIGANDS.

1 α ,25-Dihydroxyvitamin D(3) [1,25-(OH)(2)D(3)], the active metabolite of vitamin D(3), is known for the maintenance of mineral homeostasis and normal skeletal architecture. However, apart from these traditional calcium-related actions, 1,25-(OH)(2)D(3) and its synthetic analogs are being increasingly recognized for their potent antiproliferative, prodifferentiative, and immunomodulatory activities. These actions of 1,25-(OH)(2)D(3) are mediated through vitamin D receptor (VDR), which belongs to the superfamily of steroid/thyroid hormone nuclear receptors. Physiological and pharmacological actions of 1,25-(OH)(2)D(3) in various systems, along with the detection of VDR in target cells, have indicated potential therapeutic applications of VDR ligands in inflammation (rheumatoid arthritis, psoriatic arthritis), dermatological indications (psoriasis, actinic keratosis, seborrheic dermatitis, photoaging), osteoporosis (postmenopausal and steroid-induced osteoporosis), cancers (prostate, colon, breast, myelodysplasia, leukemia, head and neck squamous cell carcinoma, and basal cell carcinoma), secondary hyperparathyroidism, and autoimmune diseases (systemic lupus erythematosus, type I diabetes, multiple sclerosis, and organ transplantation). As a result, VDR ligands have been developed for the treatment of psoriasis, osteoporosis, and secondary hyperparathyroidism. Furthermore, encouraging results have been obtained with VDR ligands in clinical trials of prostate cancer and hepatocellular carcinoma. This review deals with the molecular aspects of noncalcemic actions of vitamin D analogs that account for the efficacy of VDR ligands in the above-mentioned indications.

Endocr Rev. 2005 Aug;26(5):662-87

WINTERTIME VITAMIN D DEFICIENCY IN MALE ADOLESCENTS: EFFECT ON PARATHYROID FUNCTION AND RESPONSE TO VITAMIN D3 SUPPLEMENTS.

The first part of this study consisted of an 18 month follow-up of the vitamin D status and parathyroid function in a group of 54 French male adolescents, aged from 13 to 16 years old and all pupils of a jockey training school. During the 18 month period four samplings were made, one every 6 months. The first was during September of the first year, the second and third during March and October of the second year, and the last in March of the third year. Therefore we had two main periods: summer and winter. The summer 25-hydroxyvitamin D (25(OH)D) concentrations were higher (71.6 +/- 19.9 and 52.4 +/- 16.5 nmol/l) than the winter ones (20.4 +/- 6.9 and 21.4 +/- 6.1 nmol/l). Conversely, the winter intact parathyroid hormone (iPTH) serum levels (4.18 +/- 1.18 and 4.11 +/- 1.35 pmol/l) were higher than the summer ones (2.44 +/- 0.82 and 2.71 +/- 0.71 pmol/l). At the two winter time points the 25(OH)D concentrations were lower than 25 nmol/l (10 ng/ml) in 72% (2nd year) and 68% (3rd year) of the adolescents. In the second part of the study we tried a vitamin D3 supplementation procedure designed to maintain the 25(OH)D and iPTH postsummer serum levels throughout the winter. Pairs of male adolescents matched for height, weight and Tanner pubertal stage were randomly assigned to either vitamin D3 supplementation (2.5 mg, i.e., 100,000 IU) administered orally at three specific periods (end of September, November and January) or no vitamin D3 treatment (control subjects). Blood was collected just before the first intake of vitamin D3 and 2 months after the last intake (March). The control subjects had blood drawn at the same time points. In the vitamin D3-treated subjects, the concentrations of 25 (OH)D (55.3 +/- 11.5 nmol/l) and of iPTH (3.09 +/- 1.16 pmol/l) in March and September (53.8 +/- 12.3 nmol/l and 2.75 +/- 1.26 pmol/l) were not significantly different. In the control subjects, March 25(OH)D levels (21.0 +/- nmol/l) were low, with values below 25 nmol/l in 78% of subjects, and iPTH concentrations (3.97 +/- 1.08 pmol/l) were significantly (p<0.001) higher than in September (2.91 +/- 0.81 pmol/l). The constant vitamin D wintertime deficiency and wintertime rise in iPTH in adolescent French males throughout puberty has been demonstrated. In adolescents with low dairy calcium intakes, the vitamin D3 treatment was sufficient to maintain 25(OH)D concentrations at their summer levels throughout winter and to prevent an excessive wintertime rise in iPTH levels.

Osteoporos Int. 2001;12(10):875-9

THE VITAMIN D EPIDEMIC AND ITS HEALTH CONSEQUENCES.

Vitamin D deficiency is now recognized as an epidemic in the United States. The major source of vitamin D for both children and adults is from sensible sun exposure. In the absence of sun exposure 1000 IU of cholecalciferol is required daily for both children and adults. Vitamin D deficiency causes poor mineralization of the collagen matrix in young children's bones leading to growth retardation and bone deformities known as rickets. In adults, vitamin D deficiency induces secondary hyperparathyroidism, which causes a loss of matrix and minerals, thus increasing the risk of osteoporosis and fractures. In addition, the poor mineralization of newly laid down bone matrix in adult bone results in the painful bone disease of osteomalacia. Vitamin D deficiency causes

muscle weakness, increasing the risk of falling and fractures. Vitamin D deficiency also has other serious consequences on overall health and well-being. There is mounting scientific evidence that implicates vitamin D deficiency with an increased risk of type I diabetes, multiple sclerosis, rheumatoid arthritis, hypertension, cardiovascular heart disease, and many common deadly cancers. Vigilance of one's vitamin D status by the yearly measurement of 25-hydroxyvitamin D should be part of an annual physical examination.

J Nutr. 2005 Nov;135(11):2739S-48S

VITAMIN D INTAKE AND VITAMIN D STATUS OF AUSTRALIANS.

The main source of vitamin D for Australians is exposure to sunlight. Thus, levels of serum 25-hydroxyvitamin D(3), the indicator of vitamin D status, vary according to the season and are lower at the end of winter. In Australia and New Zealand, the prevalence of vitamin D deficiency varies, but is acknowledged to be much higher than previously thought. One study found marginal deficiency in 23% of women, and another frank deficiency in 80% of dark-skinned and veiled women. The groups at greatest risk of vitamin D deficiency in Australia are dark-skinned and veiled women (particularly in pregnancy), their infants, and older persons living in residential care. Only a few foods (eg, fish with a high fat content) contain significant amounts of vitamin D. In Australia, margarine and some milk and milk products are currently fortified with vitamin D. The average estimated dietary intake of vitamin D for men is 2.6-3.0 g/day and for women is 2.0-2.2 g/day. The estimated dietary requirement of vitamin D is at least 5.0 g/day and may be higher for older people. Adequate intake of vitamin D is unlikely to be achieved through dietary means, particularly in the groups at greatest risk, although vitamin D-fortified foods may assist in maintaining vitamin D status in the general population. An appropriate health message for vitamin D needs to balance the need for sunshine against the risk of skin cancer.

Med J Aust. 2002 Aug 5;177(3):149-52

VITAMIN D STATUS AND ITS ADEQUACY IN HEALTHY DANISH PERIMENOPAUSAL WOMEN: RELATIONSHIPS TO DIETARY INTAKE, SUN EXPOSURE AND SERUM PARATHYROID HORMONE.

We conducted this study to assess the prevalence of vitamin D insufficiency in a population of normal perimenopausal women, to examine the influence of sun exposure and vitamin D intake on the concentration of 25-hydroxyvitamin D (25OHD) and to examine the association between parathyroid hormone (PTH) and 25OHD. A total of 2016 healthy women aged 45-58, who had recently undergone a natural menopause, were enrolled over a 2.5-year period in the Danish Osteoporosis Prevention Study. A marked seasonal fluctuation of 25OHD was seen, with an abrupt rise in June and high values until October. The fluctuation could be related to number of hours of sunshine per month with a two months time lag. Dietary vitamin D intake, vitamin supplementation, sunlight exposure, and use of sun-bed were all significantly related to 25OHD concentrations. Sun exposure seemed to contribute the most. The overall prevalence of vitamin D deficiency (defined as serum) was 7 %. However, in the subgroup avoiding direct sunshine and abstaining from vitamin D supplementation 32.8 % were vitamin D deficient in the winter-spring period. Although mean PTH was increased in the group with low serum 25OHD, PTH was not a sensitive marker of hypovitaminosis D in the individual, as only 16 % of those with vitamin D deficiency had PTH levels above normal range. Thus, we have shown, that healthy middle-aged Danish women are prone to vitamin D insufficiency in the winter-spring period, if they avoid sun exposure in the summer period and abstain from vitamin D supplementation.

Br J Nutr. 2001 Aug;86 Suppl 1:S97-103

VITAMIN D COMPOUNDS: CLINICAL DEVELOPMENT AS CANCER THERAPY AND PREVENTION AGENTS.

While 1,25 dihydroxycholecalciferol (calcitriol) is best recognized for its effects on bone and mineral metabolism, epidemiological data indicate that low vitamin D levels may play a role in the genesis and progression of breast, lung, colorectal and prostate cancer, as well as malignant lymphoma and melanoma. Calcitriol has strong antiproliferative effects in prostate, breast, colorectal, head/neck and lung cancer, as well as lymphoma, leukemia and myeloma model systems. Antiproliferative effects are seen in vitro and in vivo. The mechanisms of these effects are associated with G0/G1 arrest, induction of apoptosis, differentiation and modulation of growth factor-mediated signaling in tumor cells. In addition to the direct effects on tumor cells, recent data strongly support the hypothesis that the stromal effects of vitamin D analogs (e.g., direct effects on tumor vasculature) are also important in the antiproliferative effects. Antitumor effects are seen in a wide variety of tumor types and there are few data to suggest that vitamin D-based approaches are more effective in any one tumor type. Glucocorticoids potentiate the antitumor effect of calcitriol and decrease calcitriol-induced hypercalcemia. In addition, calcitriol potentiates the antitumor effects of many cytotoxic agents. Preclinical data indicate that maximal antitumor effects are seen with pharmacological doses of calcitriol and that such exposure can be safely achieved in animals using a high dose, intermittent schedule of administration. AUC and C (max) calcitriol concentrations of 32 ng.h/ml and 9.2 ng/ml are associated with striking antitumor effects in a murine squamous cell carcinoma model and there is increasing evidence from clinical trials that such exposures can be safely attained in patients. Another approach to maximizing intra-tumoral exposure to vitamin D analogs is to inhibit their catabolism. The data clearly indicate that agents which inhibit the major vitamin D catabolizing enzyme, CYP24 (24 hydroxylase), potentiate calcitriol killing of prostate tumor cells in vitro and in vivo. Phase I and II trials of calcitriol, either alone or in combination with carboplatin, taxanes

or dexamethasone, as well as the non-specific CYP24 inhibitor, ketoconazole, have been initiated in patients with androgen-dependent and -independent prostate cancer and other advanced cancers. The data indicate that high-dose calcitriol is feasible on an intermittent schedule, no dose-limiting toxicity has been encountered, but the optimal dose and schedule remain to be delineated. Clinical responses have been seen with the combination of high-dose calcitriol + dexamethasone in androgen-independent prostate cancer (AIPC) and, in a large randomized trial in men with AIPC, potentiation of the antitumor effects of docetaxel were seen.

Anticancer Res. 2006 Jul-Aug;26(4A):2551-6

VITAMIN D

The vitamin D endocrine system plays an essential role in calcium homeostasis and bone metabolism, but research during the past two decades has revealed a diverse range of biological actions that include induction of cell differentiation, inhibition of cell growth, immunomodulation, and control of other hormonal systems. Vitamin D itself is a prohormone that is metabolically converted to the active metabolite, 1,25-dihydroxyvitamin D [1,25(OH)(2)D]. This vitamin D hormone activates its cellular receptor (vitamin D receptor or VDR), which alters the transcription rates of target genes responsible for the biological responses. This review focuses on several recent developments that extend our understanding of the complexities of vitamin D metabolism and actions: the final step in the activation of vitamin D, conversion of 25-hydroxyvitamin D to 1,25(OH)(2)D in renal proximal tubules, is now known to involve facilitated uptake and intracellular delivery of the precursor to 1 α -hydroxylase. Emerging evidence using mice lacking the VDR and/or 1 α -hydroxylase indicates both 1,25(OH)(2)D(3)-dependent and -independent actions of the VDR as well as VDR-dependent and -independent actions of 1,25(OH)(2)D(3). Thus the vitamin D system may involve more than a single receptor and ligand. The presence of 1 α -hydroxylase in many target cells indicates autocrine/paracrine functions for 1,25(OH)(2)D(3) in the control of cell proliferation and differentiation. This local production of 1,25(OH)(2)D(3) is dependent on circulating precursor levels, providing a potential explanation for the association of vitamin D deficiency with various cancers and autoimmune diseases.

Am J Physiol Renal Physiol. 2005 Jul;289(1):F8-28

EPIDEMIOLOGY OF DISEASE RISKS IN RELATION TO VITAMIN D INSUFFICIENCY.

Vitamin D from ultraviolet-B (UVB) irradiance, food, and supplements is receiving increased attention lately for its role in maintaining optimal health. Although the calcemic effects of vitamin D have been known for about a century, the non-calcemic effects have been studied intently only during the past two-three decades. The strongest links to the beneficial roles of UVB and vitamin D to date are for bone and muscle conditions and diseases. There is also a preponderance of evidence from a variety of studies that vitamin D reduces the risk of colon cancer, with 1000 IU/day of vitamin D or serum 25-hydroxyvitamin D levels >33 ng/mL (82 nmol/L) associated with a 50% lower incidence of colorectal cancer. There is also reasonable evidence that vitamin D reduces the risk of breast, lung, ovarian, and prostate cancer and non-Hodgkin's lymphoma. There is weaker, primarily ecologic, evidence for the role of vitamin D in reducing the risk of an additional dozen types of cancer. There is reasonably strong ecologic and case-control evidence that vitamin D reduces the risk of autoimmune diseases including such as multiple sclerosis and type 1 diabetes mellitus, and weaker evidence for rheumatoid arthritis, osteoarthritis, type 2 diabetes mellitus, hypertension and stroke. It is noted that mechanisms whereby vitamin D exerts its effect are generally well understood for the various conditions and diseases discussed here.

Prog Biophys Mol Biol. 2006 Sep;92(1):65-79

THE ROLE OF VITAMIN D IN LEFT VENTRICULAR HYPERTROPHY AND CARDIAC FUNCTION.

The role of vitamin D in left ventricular hypertrophy and cardiac function. Cardiovascular disease is the leading cause of death among patients with end-stage renal disease (ESRD). Traditional cardiac risk factors, as well as other factors specific to the ESRD population such as hyperphosphatemia, elevated calcium and phosphate product, abnormal lipid metabolism, hyperhomocysteinemia, and chronic inflammation play a role in the excessive risk of cardiovascular death in this population. Left ventricular disorders are proven risk factors for cardiac mortality in hemodialysis patients. These disorders are present in incident ESRD patients at rates far above the general population. There is an accumulating body of evidence that suggests that vitamin D plays a role in cardiovascular disease. Abnormal vitamin metabolism, through deficiency of the active form of 1,25-dihydroxyvitamin D(3), and acquired vitamin D resistance through the uremic state, have been shown to be important in ESRD. Vitamin D deficiency has long been known to affect cardiac contractility, vascular tone, cardiac collagen content, and cardiac tissue maturation. Recent studies using vitamin D receptor deficient mice as a model demonstrate a crucial role of vitamin D in regulation of the renin-angiotensin system. Additionally, there is emerging evidence linking treatment with vitamin D to improved survival on hemodialysis and improvement in cardiac function. The emergence of this data is focusing attention on the previously underappreciated nonmineral homeostatic effects of vitamin D that very likely play an important role in the pathogenesis of cardiac disease in ESRD.

VITAMIN D AND ITS ANALOGUES: DO THEY PROTECT AGAINST CARDIOVASCULAR DISEASE IN PATIENTS WITH KIDNEY DISEASE?

BACKGROUND: Patients with chronic kidney disease (CKD) are at high risk for cardiovascular disease, and despite recent advances in hypertension control, anemia management, and dialysis adequacy, mortality remains high. Improved understanding of nontraditional risk factors, including those present at early phases in CKD, may lead to novel therapeutic strategies. CKD has been demonstrated to be an independent risk factor for cardiovascular disease in the general population, but data are lacking as to the associated potential abnormalities that occur in association with reduced glomerular filtration rate (GFR), which may contribute to this increased risk. Data are accumulating regarding the role of abnormalities of calcium, phosphorus, vitamin D, and parathyroid hormone (PTH) in cardiovascular disease. Vitamin D deficiency is present even in the early stages of CKD. Vitamin D plays a central role in calcium-phosphorus homeostasis, regulation of PTH, and formation and maintenance of bone. However, until recently, vitamin D has not been considered to have a biologic role in CKD beyond mineral regulation, or has been considered as a negative factor contributing to soft tissue and cardiovascular calcification. In light of recent observational studies showing an association of vitamin D therapy and survival benefit in hemodialysis patients, the effects of vitamin D on cardiovascular system have become a heavily debated issue. **METHODS:** A Medline search was performed to identify relevant literature describing the role of vitamin D in the pathogenesis of cardiovascular disease. Both the experimental and clinical literatures in English were reviewed. **RESULTS:** The accumulating published data demonstrate both associative relationships and mechanisms for biologic plausibility. The following three potential mechanisms may be important for the protective effects of vitamin D against cardiovascular disease mortality: vitamin D can inhibit various aspects of inflammation, which have been established as a key pathogenic mechanism in atherosclerosis; vitamin D exerts an antiproliferative effect on myocardial cell hypertrophy and proliferation, which underlies the pathogenesis of congestive heart failure; and vitamin D acts as a negative endocrine regulator for the renin-angiotensin system, which itself plays an important independent role in hypertension and cardiovascular health. **CONCLUSION:** Vitamin D deficiency might be an underestimated nonclassical risk factor for cardiovascular disease in CKD. Based on a review of the evidence, from both basic science and clinical studies, this article supports the possible protective role of vitamin D beyond its effect on mineral metabolism, and suggests the need for ongoing evaluation of the role of vitamin D in cardiovascular health in the CKD population.

Cimetidine

CONCENTRATION OF HISTAMINE IN SERUM AND TISSUES OF THE PRIMARY DUCTAL BREAST CANCERS IN WOMEN.

The aim of this study was to evaluate the concentration of histamine (HA) and the activities of their enzymes, namely histidine decarboxylase (HDC) and diaminoxydase (DAO) in 95 women with ductal breast cancer and in healthy women. The control group comprised 60 women without any pathological changes in their breasts, in whom mammoplasties were performed. In women with breast cancer the concentration of HA in serum was significantly higher than in healthy controls (9.1+/-3.2 vs. 5.9+/-3.1 nmol/l; P<0.001). The concentration of HA was significantly higher in neoplastic tissues of women with breast cancers than in unchanged tissues of healthy subjects in the control group (14.2+/-5.1 vs. 6.3+/-9.1 nmol/g; P<0.001). HDC activity was significantly elevated in cancerous tissues of women with breast cancer relative to unchanged tissues of healthy subjects (54.7+/-17.1 vs. 39.3+/-26.9 pmol/min per mg; P<0.01). However, the activity of DAO was significantly lower (14.0+/-0.4 vs. 36.1+/-9.7 pmol/min per mg; P<0.001) in neoplastic tissues than in normal tissues of healthy women. The adjacent healthy tissue of cancer revealed higher concentrations of HA than were found in unchanged tissues of healthy subjects (6.3+/-9.1 vs. 7.5+/-5.4 pmol/min per mg), but this difference did not reach statistical significance. The activity of HDC did not show any significant difference between the healthy tissues adjacent to cancer foci of women with breast cancer and normal tissues obtained from healthy subjects (39.3+/-26.9 vs. 34.5+/-24.3 pmol/min per mg). However, the activity of DAO was markedly lower than in unchanged tissues of healthy women in the control group (36.1+/-9.7 vs. 14.4+/-10.9 pmol/min per mg; P<0.001). The concentration of HA in cancerous tissues was significantly higher than in adjacent healthy tissues (14.2+/-5.1 vs. 7.5+/-5.4 nmol/g; P<0.001). The activity of HDC was significantly higher in cancerous tissues than in adjacent healthy tissues (54.7+/-17.1 vs. 34.5+/-24.3 pmol/min per mg; P<0.001), but there was no difference in the activity of DAO (14.0+/-6.4 vs. 14.4+/-10.9 pmol/min per mg). The significant elevation of HA concentration in cancerous tissues of women with the ductal breast cancers is caused by the increased synthesis and decreased inactivation of HA.

Breast. 2005 Jun;14(3):236-41

CIMETIDINE, AN UNEXPECTED ANTI-TUMOR AGENT, AND ITS POTENTIAL FOR THE TREATMENT OF GLIOBLASTOMA (REVIEW).

Cimetidine (CIM), the prototypical histamine H₂ receptor antagonist (H₂RA), was brought to market based on its ability to accelerate healing of gastrointestinal ulcers through the inhibition of gastric acid secretion. Cimetidine, the most studied H₂RA, has been demonstrated to possess anti-tumor activity against colon, gastric and kidney cancers, and melanomas. This activity involves a number of different mechanisms of action: a) CIM antagonizes tumor cell-mediated interleukin-1-induced activation of selectins in liver sinusoids, inhibiting tumor cell binding on liver sinusoids, thereby reducing the development of liver metastasis; b) histamine acts as a growth factor in various tumor cell types via the activation of H₂ receptors; CIM therefore may antagonize this effect; c) CIM acts as an immunomodulator by enhancing the host's immune response to tumor cells. With respect to malignant gliomas, CIM added to temozolomide was superior in vivo when compared to temozolomide alone in extending survival of nude mice with human glioblastoma cells orthotopically xenografted into their brain. We review the various mechanisms of action potentially associated with the therapeutic effects of CIM in the case of experimental glioblastomas, observations we hope will encourage clinical investigation of CIM in the management of highly malignant gliomas.

Int J Oncol. 2006 May;28(5):1021-30

EFFECTS OF PERIOPERATIVE CIMETIDINE ADMINISTRATION ON PERIPHERAL BLOOD LYMPHOCYTES AND TUMOR INFILTRATING LYMPHOCYTES IN PATIENTS WITH GASTROINTESTINAL CANCER: RESULTS OF A RANDOMIZED CONTROLLED CLINICAL TRIAL.

BACKGROUND/AIMS: Cimetidine (CIM) seems to have positive effects on the immune systems of cancer patients. This study was conducted to investigate the effects of perioperative administration of CIM on the peripheral blood lymphocytes, natural killer (NK) cells and tumor infiltrating lymphocytes (TIL) in patients with gastrointestinal (GI) cancer. **METHODOLOGY:** Forty-nine GI cancer patients were randomized into a treatment group which took CIM in the perioperative period, and a control group which did not take the drug. The treatment was initiated 7 days (d) before operation and continued until 10 d after surgery. At baseline examination, before operation, on the 2nd and the 10th postoperative d, peripheral blood T lymphocytes, helper T cells, T suppressor cells, and NK cells were measured by immunocytochemical method. The surgical specimens were examined for TIL

response, and immunohistochemical study was performed to measure the proportion of T and B lymphocytes in the TIL population. RESULTS: In comparison with normal controls, both the treatment and the control groups had decreased T cells, helper T cells and NK cells at baseline. In the control group, total T cells, helper T cells and NK cells declined progressively with the disease course and the decreases became more profound after operation. From the baseline to the 2nd postoperative d, the proportion of total T cells, helper T cells, and NK cells went down from 60.5+/-4.6 to 56.2+/-3.8 percent, from 33.4+/-3.7 to 28.1+/-3.4 percent, and from 15.0+/-2.8 to 14.2+/-2.2 percent, respectively. On the other hand, there were significant improvements in these parameters after CIM treatment. On the 10th postoperative d, the treatment group had significantly higher percentages of total T cells, helper T cells and NK cells than control group. Moreover, CIM treatment also boosted the TIL response, as was reflected by findings that 68% (17/25) of the patients in the treatment group had significant TIL responses and only 25% (6/24) of the cases had discernible TIL response. CONCLUSIONS: Perioperative application of CIM to GI cancer patients could help restore the diminished cellular immunity boost TIL responses to tumor.

Hepatogastroenterology. 2005 Mar-Apr;52(62):504-8

THE EFFECT OF CIMETIDINE MAINLY INCREASES CD4+ CELLS OF PERIPHERAL BLOOD T LYMPHOCYTES

Cimetidine, one of the most popular histamine-2 receptor antagonists, has been reported to improve survival in gastrointestinal cancer patients and to activate cell-mediated immune response in surgical patients. NKT cells are a population of T cells that share characteristics with natural killer cells, and their main functions are production of immunoregulatory cytokines and cytolytic activities. In this study, we aimed to investigate the effect of cimetidine on the cell-mediated immunoresponse. Six healthy adult volunteers were given 800 mg of cimetidine per day orally, and their blood samples were taken prior to and at days 1, 3, 5, and 7 days post-administration of cimetidine. Leukocyte counts and differentials were obtained by the conventional hemogram, and the leukocyte subsets were analyzed by flow cytometry. Cimetidine administration caused leukocytosis, dependent on the increase of neutrophils, as well as of the CD3-positive T lymphocytes, and the subset of CD4-positive cells among them. On the other hand, the NK cell subpopulation was decreased, and the NKT cell subpopulation was not affected. The present results suggest that cimetidine is a modulator of the cellular immunity, and may be used as the activator of the tumor specific immunoresponse.

Gan To Kagaku Ryoho. 2005 Oct;32(11):1576-7

CIMETIDINE INHIBITS ANGIOGENESIS AND SUPPRESSES TUMOR GROWTH.

Cimetidine, a histamine type-2 receptor antagonist, has been reported to improve survival of patients with cancers. However, the exact mechanisms by which cimetidine suppresses development of cancers remain to be elucidated. Solid tumors require neovascularization for their growth. Here, we investigated the effects of cimetidine on tumor growth and angiogenesis. Syngeneic colon cancer cells, CMT93 cells, were inoculated into the subcutaneous space of C57BL/6 mice. Mice were treated with either saline or cimetidine. Tumor size was measured everyday and angiogenesis was evaluated histologically. Cimetidine markedly suppressed tumor growth with reduced neovascularization in the tumor. Cimetidine had no effect on proliferation of CMT93 cells in vitro. Vascular endothelial growth factor production by cancer cells was not affected by cimetidine, while vascular-like tube formation by endothelial cells in vitro was significantly impaired in the presence of cimetidine. Our findings suggest that cimetidine suppresses tumor growth, at least in part, by inhibiting tumor-associated angiogenesis.

Biomed Pharmacother. 2005 Jan-Feb;59(1-2):56-60

EFFECTS OF CIMETIDINE ON THE BIOLOGICAL BEHAVIORS OF HUMAN GASTRIC CANCER CELLS

OBJECTIVE: To investigate the effects of cimetidine on the proliferation, apoptosis, adhesion, and invasion of human gastric cancer cells. METHODS: Human gastric cancer cells of the line SGC-790 were cultured. Cimetidine of the concentrations of different concentrations was added into the culture fluid. The survival rate of the cells was calculated. Flow cytometry was used to examine the distribution of cell cycle and apoptosis of the cells. Fluorescence staining was used to observe the morphology of the apoptotic cells. The adhesion of the cells was measured by MTT method and their invasion ability was tested with Millicell chambers. RESULTS: The proliferation of the AGC-7901 cells was inhibited by cimetidine of the concentration of 0.5 to 5 mmol/L time and dose-dependently. Cimetidine of the concentrations of 0.5 - 10 mmol/L retarded the SGC-7901 cells at the stage G(0)/G(1) and increased the number of apoptotic cells dose-dependently (P < 0.05). Cimetidine of the non-toxic concentrations 250, 125, and 62.5 micrommol/L decreased the adhesion and invasion of the SGC-7901 cells to the extracellular matrix. CONCLUSION: Capable of inducing apoptosis and cell cycle arrest, cimetidine is helpful in treatment of cancers of gastric cancer.

Zhonghua Yi Xue Za Zhi. 2006 Jul 11;86(26):1813-6

RAPID INDUCTION OF CYTOKINE AND E-SELECTIN EXPRESSION IN THE LIVER IN RESPONSE TO METASTATIC TUMOR CELLS.

The cytokine-inducible endothelial cell adhesion receptor E-selectin has been implicated in cancer metastasis. Previously, we reported that experimental liver metastasis of Lewis lung carcinoma subline H-59 cells could be abrogated in animals treated with an anti-E-selectin antibody. To gain further insight into the functional relevance of E-selectin expression to liver colonization, we investigated here the time course of cytokine and hepatic E-selectin expression after the intrasplenic/portal inoculation of H-59 cells by using a combination of reverse transcription-PCR, Northern blot analysis, immunohistochemistry, and in situ hybridization. In parallel, we analyzed cytokine induction in response to the injection of Lewis lung carcinoma subline M-27 and murine melanoma B16-F1 cells, which do not spontaneously metastasize to the liver. In livers derived from normal or saline-injected mice, only minimal basal levels of TNF-alpha and IL-1 mRNA were detectable by RT-PCR. Rapid cytokine mRNA induction was noted within 30-60 min of H-59 injection, reaching maximal levels at 4-6 h. This was followed by the appearance of E-selectin mRNA, which was detectable at 2 h after injection and reached maximal levels at 6-8 h, declining to basal levels by 24 h. In situ hybridization analysis and immunohistochemistry localized E-selectin mRNA and protein, respectively, to the sinusoidal endothelium. M-27 cells failed to induce cytokine or E-selectin expression, whereas B-16 cells elicited a delayed and more short-lived response. The results demonstrate that upon entry into the hepatic circulation, tumor cells can rapidly trigger a molecular cascade leading to the induction of E-selectin expression on the sinusoidal endothelium and suggest that E-selectin induction may contribute to the liver-colonizing potential of tumor cells.

Cancer Res. 1999 Mar 15;59(6):1356-61

CIMETIDINE INHIBITS CANCER CELL ADHESION TO ENDOTHELIAL CELLS AND PREVENTS METASTASIS BY BLOCKING E-SELECTIN EXPRESSION.

Although the beneficial effect of cimetidine on survival in cancer has been clinically demonstrated in colorectal cancer patients, the mode of action of cimetidine has not been elucidated. In this report, we have demonstrated for the first time that cimetidine can block the adhesion of a colorectal tumor cell line to the endothelial cell monolayer in cell culture and that it can suppress the metastasis of the tumor cell in a nude mouse model. We also demonstrated that these antimetastasis effects of cimetidine might occur through down-regulation of the cell surface expression of E-selectin on endothelial cells, a ligand for sialyl Lewis antigens on tumor cells. We found that the cimetidine-mediated down-regulation of E-selectin did not involve down-regulation of E-selectin mRNA or blocking of the nuclear translocation of nuclear factor kappaB, a transcriptional activator of E-selectin gene expression. Because two other histamine type 2 receptor antagonists, famotidine and ranitidine, did not show any similar effect, these actions of cimetidine probably do not occur via blocking of the histamine receptor. These observations support the idea that cancer metastasis can be blocked by cimetidine administration through blocking the adhesion of tumor cells to the endothelium when an interaction between E-selectin and sialyl-Lewis antigens plays a role.

Cancer Res. 2000 Jul 15;60(14):3978-84

CIMETIDINE INHIBITS THE ADHESION OF CANCER CELLS WITH SIALYL LEWIS EPI TOPE ONTO THE VASCULAR ENDOTHELIUM

The attachment of circulating cancer cells to vascular endothelium is considered an important initial step in hematogenous metastasis. We believe that hematogenous metastasis can be inhibited by blocking the adhesion of cancer cells to vascular endothelium. We demonstrated that cimetidine suppressed the expression of E-selectin on the surface of HUVECs, which was a ligand to the sialyl Lewis (sLe) epitope. Thereby, adhesion of HT-29 cells to HUVECs was inhibited by cimetidine pretreatment. In this study, adhesion between cancer cells and HUVECs was observed by a high-speed video recording system. We examined whether or not cimetidine inhibited the adhesion of cancer cells with the sLe epitope, such as gastric, esophageal and breast cancers, to HUVECs. Cimetidine was able to block the adhesion of gastric, esophageal and breast cancer cells with the sLe epitope. We conclude that cimetidine would be effective for inhibiting hematogenous metastasis on gastric, esophageal and breast cancer cells with the expression of sLe epitope.

Gan To Kagaku Ryoho. 2003 Oct;30(11):1788-90

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