NUTRIENTES BÁSICOS Y CÁNCER

El cáncer es una patología de primer orden en la sociedad occidental. En términos generales, el cáncer surge del daño continuo del ADN y/o de la expresión inadecuada de los genes fundamentales, lo que genera que estas células proliferen de manera descontrolada y den lugar a modificaciones de la forma, tamaño y función del tejido afectado.

Los alimentos pueden ser factores etiológicos del cáncer, de manera que algunos factores dietéticos pueden aumentar o disminuir el riesgo de padecer ciertos tipos de cáncer. El consumo excesivo de grasas en la dieta se ha relacionado con una mayor probabilidad de la aparición de cáncer de mama, colon, pulmón y próstata. Una dieta con exceso de proteínas, principalmente de origen animal, se ha relacionado con un aumento de la incidencia de cáncer de colon y próstata. El alcohol es un factor de riesgo importante para la aparición de tumores de diversos tipos, y la combinación de alcohol y tabaco, tiene un efecto sinérgico sobre el riesgo de padecer un tumor, y en concreto con cáncer colorectal. En cambio, el consumo de al menos cinco porciones de frutas y vegetales de forma diaria ha sido asociado con una incidencia de cáncer disminuida. Las frutas y verduras son una excelente fuente de vitaminas, minerales y otros fitoquímicos, lo que podría jugar un papel en su efecto anticarcinogénico.

El papel de la **vitamina C** en la prevención del cáncer es muy amplio. La mayoría ha demostrado que ingestas más altas de vitamina C están asociadas con una incidencia disminuida de cánceres de boca, garganta y cuerdas vocales, esófago, estómago, colon-recto y pulmón. En general, los estudios prospectivos en los que los grupos con la ingesta más baja consumieron más de 86 mg/día de vitamina C a diario no han encontrado diferencias en el riesgo de cáncer, mientras que los estudios que encontraron reducciones significativas del riesgo de cáncer las encontraron en personas que consumían diariamente al menos 80 a 110 mg de vitamina C. Otro papel demostrado de dosis elevadas de ácido ascórbico es que aumenta la concentración intracelular de glutatión, incrementa la actividad de la enzima glutatión-S-transferasa que se corresponde a una mayor absorción de cisteína.

La **vitamina E** y sus formas (α-, β-, γ-, δ-) tocoferol y (α-, β-, γ-, δ-) tocotrienol han demostrado tener relación en la prevención del cáncer y la inhibición tumoral, tanto in vitro como in vivo. La vitamina E presenta la eficiencia contra diferentes tipos específicos de cáncer de pulmón y ser un preventivo en hombres con elevado riesgo de padecer cáncer prostático. La evidencia también indica que el tratamiento combinado de tocotrienol con otras quimioterapias puede resultar en una inhibición sinérgica del crecimiento de células cancerosas. Esto puede proporcionar importantes beneficios para la salud en la prevención y / o tratamiento del cáncer cuando se utiliza ya sea solo como monoterapia o en combinación con otros agentes anticancerosos.

Varios tumores malignos contienen receptores de **vitamina D** (RVD), incluyendo cánceres de mama, pulmón, piel (melanoma), colon, y hueso. Se ha encontrado que las formas

biológicamente activas de la vitamina D, como la 1,25-dihidroxivitamina D y sus análogas, inducen la diferenciación celular y/o inhiben la proliferación de una serie de tipos celulares cancerígenos y no cancerígenos mantenidos en cultivo celular.

Algunos estudios han reportado que ingestas de vitamina D y niveles plasmáticos de 25- (OH) vitamina D más altos, se asocian con reducciones en el riesgo de cáncer colonorectal. Un estudio de cinco años de más de 120,000 personas encontró que los hombres con las ingestas más altas de vitamina D tenían un riesgo de cáncer colonorectal que era un 29% más bajo que el de los hombres con las ingestas más bajas de vitamina D. Según un análisis de dosis-respuesta reciente, se estimó que 1,000 UI de vitamina D oral a diario reducirían el riesgo personal de cáncer colonorectal en 50%.

Debido a las importantes funciones que desempeña el **folato** en la síntesis y metilación del ADN y ARN, la ingesta de folato afecta tanto a la reparación del ADN como la expresión de los genes. Niveles de folato disminuidos están asociados con cáncer de cuello uterino, colon y recto, pulmón, esófago, cerebro, páncreas y mama. Estudios observacionales indican que una ingesta de folato relativamente baja, y una ingesta elevada de alcohol se asocian con incidencia aumentada de cáncer colonorectal. En un estudio prospectivo de más de 45,000 hombres, la ingesta regular de más de dos bebidas alcohólicas por día duplicó el riesgo de cáncer de colon. Sin embargo, una ingesta de alcohol aumentada en individuos que consumieron 650 mcg o más de folato por día, no se asoció con un riesgo aumentado de cáncer de colon. Otro punto importante son los diferentes polimorfismos que puede tener el enzima metilentetrahidrofolato reductasa (MTHFR). En una revisión sistemática se analizaron 10 estudios que relacionaban la ingesta de folato (dietético y en forma de suplemento) con el cáncer de páncreas. Los resultados obtenidos muestran que una mayor ingesta de folato se asocia a un menor riesgo de padecer cáncer y que los folatos pueden desempeñar un papel protector en la carcinogénesis del cáncer de páncreas. La forma L-metilfolato, es la forma activa de los folatos, no necesita pasar por ninguna activación previa para incorporarse en las rutas metabólcas. Es 7 veces más biodisponible que el ácido fólico u otros folatos, lo que permite bajar dosis y asegurarse de su actividad y eficacia.

La deficiencia de **vitamina B12** deja al folato en una forma que es inutilizable para el cuerpo en la síntesis de ADN. Tanto la deficiencia de vitamina B12, como la deficiencia de folato, derivan en una capacidad disminuida para las reacciones de metilación. De esta forma, la deficiencia de vitamina B12 podría conducir a una mayor tasa de daño oxidativo y a una alterada metilación del ADN, los cuales son factores importantes del riesgo de cáncer. En adultos jóvenes y en hombres mayores señaló los niveles incrementados de homocisteína y los niveles disminuidos de vitamina B12 en la sangre se asocian con un biomarcador de la ruptura de cromosomas en leucocitos. En un estudio de doble ciego controlado con placebo, se minimizó el mismo marcador de ruptura de cromosomas en adultos jóvenes suplementando diariamente con 700 mcg de ácido fólico y 7 mcg de vitamina B12.

La deficiencia de **tiamina** en algunos pacientes oncológicos con tumores de crecimiento rápido. No obstante, la investigación en células de cultivo y en modelos animales señala que las células cancerígenas que se dividen rápidamente tienen un requerimiento de tiamina

elevado. Todas las células que se dividen rápidamente necesitan ácidos nucleicos a un ritmo aumentado, pero algunas células cancerígenas parecen depender fuertemente en la enzima dependiente de TPP, transcetolasa, para proveer la ribosa-5-fosfato necesaria para la síntesis de ácidos nucleicos. La suplementación con tiamina es común en pacientes con cáncer para prevenir una deficiencia de tiamina, pero Boros et al. advierten que demasiada tiamina podría de hecho estimular el crecimiento de algunos tumores malignos, sugiriendo que la suplementación con tiamina se reserve para aquellos pacientes con cáncer que sean efectivamente deficientes de tiamina. En la actualidad no existe evidencia disponible de estudios en humanos que apoye o refute esta teoría.

Estudios de cultivos celulares (*in vitro*) aportan evidencia de que el contenido de **NADH** influencia la respuesta celular ante el daño del ADN, un factor de riesgo importante en el desarrollo del cáncer. El NAD celular se consume en la síntesis de polímeros de ADP-ribosa, los que juegan un papel en la reparación del ADN, y en polímeros de ADP-ribosa cíclicos que podrían también mediar importantes vías de señalización celular en la prevención del cáncer. Adicionalmente, se ha encontrado que el agotamiento celular del NAD disminuye los niveles de la proteína supresora de tumores, p53, en células de mama, piel y pulmón humanos. Un estudio de casos y controles de gran tamaño encontró que un consumo aumentado de **niacina**, junto con nutrientes antioxidantes, se asociaba con una incidencia disminuida de cáncer oral (boca), faríngeo (garganta), y esofágico en el norte de Italia y Suiza. Un aumento de la ingesta de niacina de 6.2 mg se asoció con un descenso de cerca del 40% de los casos de cáncer de boca y garganta.

El **zinc** mejora las funciones del sistema inmune, pero también funciona como un antioxidante y agente anti-inflamatorio. El estrés oxidativo y la inflamación crónica han sido implicados en el desarrollo de muchos tipos de cáncer. En un estudio realizado con pacientes con cáncer de cabeza y cuello, se demostró que casi el 65% de estos pacientes tenían deficiencia de zinc basado en sus concentraciones de zinc celulares. Actividad de las NK y la IL-2 también se vieron afectadas por su deficiencia. El estado del zinc también se correlacionó con el número de ingresos hospitalarios y la incidencia de infecciones. Los suplementos de zinc pueden tener efectos beneficiosos sobre el cáncer por la disminución de la angiogénesis, la inducción de citocinas inflamatorias y el aumento de la apoptosis en las células cancerosas.

Los resultados de estudios epidemiológicos sobre la incidencia de cáncer y el bajo consumo de **selenio** son poco consistentes y muestran una gran variedad de resultados, ya que relacionan diferentes individuos (sexo, edad, otras enfermedades…) con la amplia variedad de cánceres. En cambio estudios más concretos, muestran que una ingesta deficiente de selenio incrementa el riesgo de cáncer prostático. Un estudio realizado en 50.000 hombres en US encontró una relación inversamente significativa entre el bajo contenido de selenio (uñas del pie) y el riesgo a padecer cáncer prostático. También se han realizado estudios donde se combina fármacos como las sulfonamidas con selenio, mejorando la eficacia y disminuyendo los efectos indeseados del fármaco. El selenio parece tener un efecto protector en las diversas etapas del cáncer debido a su propiedad antioxidante, mejora la desintoxicación carcinógeno y evita la invasión de células mediante la inhibición de la angiogénesis.

Otros nutrientes como el **ácido alfa lipoico** pueden controlar y limitar la cantidad de radicales libres influyendo en el desarrollo de patologías como el cáncer. La revisión de los trabajos publicados pone de manifiesto el efecto positivo del ácido alfa lipoico en el control de la apoptosis celular en diferentes tipos de cáncer mediante un aumento de las especies reactivas al oxígeno así como un retardo en el crecimiento de las mismas. Además se ha demostrado su capacidad antioxidante y su potencial para regenerar otros antioxidantes. La revisión concluye que el ácido alfa lipoico tiene un papel significativo como oxidante y prooxidante en el cáncer y las patologías de sensibilización central. Otros estudios muestran la capacidad que tiene el ácido R lipoico en estabilizar la actividad del factor nuclear kappaB (NF (k) B) y atenúa la liberación de radicales libres, citoquinas citotóxicas y evita la expresión de oncogenes. El ácido lipoico (y su forma reducida ácido dihidrolipoico), cumple con todos los criterios para ser un antioxidante ideal, ya que puede neutralizar fácilmente radicales libres, quelar metales, tiene un carácter amfifílico y no presenta ningún efecto secundario grave. Los estudios actuales apoyan su uso en el tratamiento auxiliar de muchas enfermedades , como la diabetes , las enfermedades autoinmunes , cardiovasculares , neurodegenerativas y cáncer.

La **coenzima Q10,** presente de forma mayoritaria en las membranas de las mitocondrias, se ha puesto de manifiesto que su concentración disminuye con la edad, que determinados fármacos como las estatinas inhiben su biosíntesis y que su concentración es baja en pacientes con enfermedades crónicas. Es una molécula esencial para la cadena de transporte electrónico y mejora la fatiga y cansancio. Existen estudios publicados sobre la suplementación y su efecto en la reducción del riesgo de determinados cánceres como el de próstata, llegando a la conclusión que sí podría reducir el riesgo. Otro estudio realizado en pacientes con cáncer de pulmón muestra que la concentración de conezima Q10 es significativamente menor en el grupo con cáncer de pulmón que los del grupo control, lo que significa que una suplementación podría ser beneficiosa para dicho grupo.

VITAMINA C

VITAMINA C

PLoS One. 2009;4(2):e4409. doi: 10.1371/journal.pone.0004409. Epub 2009 Feb 6.

Antiproliferative effect of ascorbic acid is associated with the inhibition of genes necessary to cell cycle progression.

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Source

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Abstract

BACKGROUND:

Ascorbic acid (AA), or Vitamin C, is most well known as a nutritional supplement with antioxidant properties. Recently, we demonstrated that high concentrations of AA act on PMP22 gene expression and partially correct the Charcot-Marie-Tooth disease phenotype in a mouse model. This is due to the capacity of AA, but not other antioxidants, to down-modulate cAMP intracellular concentration by a competitive inhibition of the adenylate cyclase enzymatic activity. Because of the critical role of cAMP in intracellular signalling, we decided to explore the possibility that ascorbic acid could modulate the expression of other genes.

METHODS AND FINDINGS:

Using human pangenomic microarrays, we found that AA inhibited the expression of two categories of genes necessary for cell cycle progression, tRNA synthetases and translation initiation factor subunits. In in vitro assays, we demonstrated that AA induced the S-phase arrest of proliferative normal and tumor cells. Highest concentrations of AA leaded to necrotic cell death. However, quiescent cells were not susceptible to AA toxicity, suggesting the blockage of protein synthesis was mainly detrimental in metabolically-active cells. Using animal models, we found that high concentrations of AA inhibited tumor progression in nude mice grafted with HT29 cells (derived from human colon carcinoma). Consistently, expression of tRNA synthetases and ieF2 appeared to be specifically decreased in tumors upon AA treatment.

CONCLUSIONS:

AA has an antiproliferative activity, at elevated concentration that could be obtained using IV injection. This activity has been observed in vitro as well in vivo and likely results from the inhibition of expression of genes involved in protein synthesis. Implications for a clinical use in anticancer therapies will be discussed

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Ascorbic acid derivatives as a new class of antiproliferative molecules.

Bordignon B, Chiron J, Fontes M.

Source

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Abstract

Ascorbic acid (AA) has long been described as an antiproliferative agent. However, the molecule has to be used at a very high concentrations, which necessitates i.v. injection, and the tight regulation of in-blood and in-cell AA concentrations making it impossible to hold very high concentrations for any substantial length of time. Here we report evidence that AA derivates are antiproliferative and cytotoxic molecules at an IC_{50} lower than AA itself. Among these new molecules, we selected K873 that has cytotoxic and antiproliferative effects on different human tumor cells at tenth micromolar concentration. In a further step, we demonstrated that K873 selectively to kills only cancer cells without being toxic for normal non-dividing (or poorly dividing) cells. Finally, we tested the effect of treatment with K873 (5-10mg/kg/d by i.p. route) on tumor progression in xenografted immunodeficient mice (BALB/c Nude). Our data suggest that K873 administration strongly inhibits tumor progression. In a previous study using microarrays, we demonstrated that AA decreases the expression of two genes families involved in cell cycle progression, i.e. initiation factor of translation and tRNA synthetases. Here we show that K873 treatment also decreases the expression of four of these genes in xenografted tumors, in proportions similar to that previously observed with AA. Taken together, our data suggest that AA and K873 share similar action. Our findings suggest that AA derivatives could be a promising new class of anti-cancer drugs, either alone or in combination with other molecules.

J Nutr Biochem. 2006 Jul;17(7):454-62. Epub 2005 Nov 15.

Retinoic acid and ascorbic acid act synergistically in inhibiting human breast cancer cell proliferation.

Kim KN, Pie JE, Park JH, Park YH, Kim HW, Kim MK.

Source

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Abstract

BACKGROUND:

Breast cancer is an increasingly common malignancy. Several vitamins such as retinoic acid (RA), ascorbic acid (AA), vitamin D and vitamin E are known to prevent the development and progression of breast cancer.

OBJECTIVE:

We sought to determine whether RA and AA together (RA+AA) acted synergistically in blocking the proliferation of human breast cancer cells. To elucidate the mechanism by which RA+AA inhibited breast carcinoma proliferation, we then evaluated the gene expression profiles of the treated and untreated cells by radioactive cDNA microarray analysis.

METHODS:

We cultured the human breast cancer cell line MCF-7 for 3 days with 100 nM RA and/or 1 mM AA, counted the cell numbers and harvested the total RNAs for cDNA microarray analysis.

RESULTS:

RA, AA and RA+AA reduced MCF-7 cell proliferation by 20.7%, 23.3% and 75.7% relative to the untreated cell proliferation, respectively. The synergistic ratio of RA and AA was 1.72. The MCF-7 gene expression profiles showed that 29 genes were up-regulated and 38 genes were down-regulated after RA+AA treatment. The nature of these genes suggests that the mechanism by which RA and AA act synergistically in inhibiting human breast cancer cell proliferation may involve the expression of genes that induce differentiation and block proliferation, and the up-regulation of antioxidant enzymes and proteins involved in apoptosis, cell cycle regulation and DNA repair.

CONCLUSION:

Combined treatment with RA and AA inhibits the proliferation of human breast cancer cells by altering their gene expression related to antioxidation processes as well as the proliferation inhibitory pathway.

Nutrients. 2013 Sep 9;5(9):3496-505. doi: 10.3390/nu5093496.

The effects of high concentrations of vitamin C on cancer cells.

Park S.

Source

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Abstract

The effect of high doses of vitamin C for the treatment of cancer has been controversial. Our previous studies, and studies by others, have reported that vitamin C at concentrations of 0.25-1.0 mM induced a dose- and time-dependent inhibition of proliferation in acute myeloid leukemia (AML) cell lines and in leukemic cells from peripheral blood specimens obtained from patients with AML. Treatment of cells with high doses of vitamin C resulted in an immediate increase in intracellular total glutathione content and glutathione-S transferase activity that was accompanied by the uptake of cysteine. These results suggest a new role for high concentrations of vitamin C in modulation of intracellular sulfur containing compounds, such as glutathione and cysteine. This review, discussing biochemical pharmacologic studies,

including pharmacogenomic and pharmacoproteomic studies, presents the different pharmacological effects of vitamin C currently under investigation

Int J Biochem Cell Biol. 2004 Nov;36(11):2180-95.

L-Ascorbic acid induces apoptosis in acute myeloid leukemia cells via hydrogen peroxide-mediated mechanisms.

Park S, Han SS, Park CH, Hahm ER, Lee SJ, Park HK, Lee SH, Kim WS, Jung CW, Park K, Riordan HD, Kimler BF, Kim K, Lee JH.

Source

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Abstract

L-Ascorbic acid (LAA) is being investigated clinically for the treatment of patients with acute myeloid leukemia (AML) based on the observed effects of LAA on AML progenitor cells in vitro. However, the mechanism for LAA-induced cytoreduction remains to be elucidated. LAA at concentrations of 0.25-1.0 mM induced a dose- and time-dependent inhibition of proliferation in three AML cell lines and also in leukemic cells from peripheral blood specimens obtained from three patients with AML. In contrast, ovarian cancer cell lines were only minimally affected. Flow cytometric analysis showed that LAA at concentrations of 0.25-1.0 mM could significantly induce apoptosis in the AML cell lines. LAA induced oxidation of glutathione to oxidized form (GSSG) and subsequent H(2)O(2) accumulation in a concentration-dependent manner, in parallel to induction of apoptosis. The direct role of H(2)O(2) in the induction of apoptosis in AML cells was clearly demonstrated by the finding that catalase could completely abrogate LAA-induced apoptosis. Induction of apoptosis in LAA-treated AML cells involved a dose-dependent increase of Bax protein, release of cytochrome C from mitochondria to cytosol, activation of caspase 9 and caspase 3, and cleavage of poly[ADP-ribose]polymerase. In conclusion, LAA can induce apoptosis in AML cells, and this is clearly due to H(2)O(2) which accumulates intracellularly as a result of oxidation of reduced glutathione by LAA

VITAMINA E

J Thorac Dis. 2013 Jun;5(3):349-52. doi: 10.3978/j.issn.2072-1439.2013.04.03.

Tocopherols and tocotrienols as anticancer treatment for lung cancer: future nutrition.

Zarogoulidis P, Cheva A, Zarampouka K, Huang H, Li C, Huang Y, Katsikogiannis N, Zarogoulidis K.

Source

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Abstract

Nutrition has been known for ages to shield the immune system against several formulations that deregulate normal DNA repair mechanisms, and induce tumorigenesis. Vitamins and in specific Vit E and its members tocopherols (α-, β-, γ-, δ-) and tocotrienols (α-, β-, γ-, δ-) have demonstrated strong association with the prevention of cancer and inhibition of tumor, both in vitro and in vivo. Vitamin E has also demonstrated effective role against chemotherapy resistant cancer cell evolution and a protective role in acute interstitial disease. Several formulations of Vitamin E have been investigated conjugated with different carriers as nano-formulations and administered in different forms. Additionally, several tumorigenic pathways have been investigated separately in an effort to identify which member of Vitamin E inhibits efficiently every pathway. Vitamin E presented efficiency against specific subhistology types of lung cancer. Finally, in the current work up to date information regarding novel formulations with Vitamin E and inhibition pathways are going to be presented and commented.

Potential role of tocotrienols in the treatment and prevention of breast cancer.

Sylvester PW, Akl MR, Malaviya A, Parajuli P, Ananthula S, Tiwari RV, Ayoub NM.

Source

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Abstract

Vitamin E is a generic term that refers to a family of compounds that is further divided into two subgroups called tocopherols and tocotrienols. Although all natural forms of vitamin E display potent antioxidant activity, tocotrienols are significantly more potent than tocopherols in inhibiting tumor cell growth and viability, and anticancer activity of tocotrienols is mediated independently of their antioxidant activity. In addition, the anticancer effects of tocotrienols are observed using treatment doses that have little or no effect on normal cell function or viability. This review will summarize experimental studies that have identified the intracellular mechanism mediating the anticancer effects of tocotrienols. Evidence is also provided showing

that combined treatment of tocotrienol with other cancer chemotherapies can result in a synergistic inhibition in cancer cell growth and viability. Taken together, these findings strongly indicate that tocotrienols may provide significant health benefits in the prevention and/or treatment of cancer when used either alone as monotherapy or in combination with other anticancer agents.

BMC Cancer. 2013 Jun 13;13:285. doi: 10.1186/1471-2407-13-285.

Mitochondria-targeted vitamin E analogs inhibit breast cancer cell energy metabolism and promote cell death.

Cheng G, Zielonka J, McAllister DM, Mackinnon AC Jr, Joseph J, Dwinell MB, Kalyanaraman B.

Source

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Abstract

BACKGROUND:

Recent research has revealed that targeting mitochondrial bioenergetic metabolism is a promising chemotherapeutic strategy. Key to successful implementation of this chemotherapeutic strategy is the use of new and improved mitochondria-targeted cationic agents that selectively inhibit energy metabolism in breast cancer cells, while exerting little or no long-term cytotoxic effect in normal cells.

METHODS:

In this study, we investigated the cytotoxicity and alterations in bioenergetic metabolism induced by mitochondria-targeted vitamin E analog (Mito-chromanol, Mito-ChM) and its acetylated ester analog (Mito-ChMAc). Assays of cell death, colony formation, mitochondrial bioenergetic function, intracellular ATP levels, intracellular and tissue concentrations of tested compounds, and in vivo tumor growth were performed.

RESULTS:

Both Mito-ChM and Mito-ChMAc selectively depleted intracellular ATP and caused prolonged inhibition of ATP-linked oxygen consumption rate in breast cancer cells, but not in non-cancerous cells. These effects were significantly augmented by inhibition of glycolysis. Mito-ChM and Mito-ChMAc exhibited anti-proliferative effects and cytotoxicity in several breast cancer cells with different genetic background. Furthermore, Mito-ChM selectively accumulated in tumor tissue and inhibited tumor growth in a xenograft model of human breast cancer.

CONCLUSIONS:

We conclude that mitochondria-targeted small molecular weight chromanols exhibit selective anti-proliferative effects and cytotoxicity in multiple breast cancer cells, and that esterification of the hydroxyl group in mito-chromanols is not a critical requirement for its anti-proliferative and cytotoxic effect

Nucl Med Commun. 2013 Aug;34(8):777-86. doi: 10.1097/MNM.0b013e328362b1f2.

Does vitamin E protect salivary glands from I-131 radiation damage in patients with thyroid cancer?

Fallahi B, Beiki D, Abedi SM, Saghari M, Fard-Esfahani A, Akhzari F, Mokarami B, Eftekhari M.

Source

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Abstract

OBJECTIVES:

Salivary gland impairment after high-dose radioiodine (I) treatment is well recognized. The aim of this study was to determine the protective effect of vitamin E on radiation-induced salivary gland dysfunction in patients undergoing I treatment for differentiated thyroid cancer.

METHODS:

Thirty-six patients with differentiated thyroid carcinoma were enrolled in this study. They were randomly divided into two groups before postsurgical ablation therapy with 3700-5550 MBq I: the control group, comprising 17 patients, and the vitamin E group, comprising 19 patients. All 19 patients in the experimental group received vitamin E at a dose of 800 IU/day for a duration of 1 week before to 4 weeks after I therapy and the 17 patients in the control group received a placebo for the same duration. Salivary gland function was assessed using salivary gland scintigraphy with intravenous injection of 370 MBq Tc-pertechnetate in two phases, one immediately before and the other 6 months after I ablative therapy. First-minute uptake ratio, maximum uptake ratio, maximum secretion percentage, and excretion fraction (EF) of each salivary gland were measured and compared between the study phases for the two groups.

RESULTS:

There was no significant difference between preablative and postablative salivary scintigraphic indices in the experimental vitamin E group, whereas maximum secretion percentage and EF of the right submandibular gland and EF of the left parotid gland were significantly decreased in the control group. There was also a higher significant decrease in the EF of the left parotid gland in the control group compared with the vitamin E group.

CONCLUSION:

Vitamin E consumption may be associated with a significant protective effect against radiation-induced dysfunction in salivary glands following single-dose I therapy in patients with differentiated thyroid cancer.

Ann Saudi Med. 2007 Nov-Dec;27(6):409-14.

The role of vitamin E in the prevention of cancer: a meta-analysis of randomized controlled trials.

Alkhenizan A, Hafez K.

Source

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Abstract

BACKGROUND:

There are conflicting results in published randomized controlled trials (RCTs) on the role of vitamin E in the prevention of cancer. We conducted a meta-analysis of RCTs to evaluate the role of vitamin E in the prevention of cancer in adults.

METHODS:

We included RCTs in which the outcomes of the intake of vitamin E supplement alone or with other supplements were compared to a control group. The primary outcomes were total mortality, cancer mortality, total incidence of cancer, and incidence of lung, stomach, esophageal, pancreatic, prostate, breast and thyroid cancers. All identified trials were reviewed independently by the two reviewers to determine whether trials should be included or excluded. The quality of all included studies was scored independently by the two reviewers.

RESULTS:

Twelve studies, which included 167025 participants, met the inclusion criteria. There were no statistically significant differences in total mortality (relative risk, 0.99; 95% CI, 0.96-1.03) among the different groups of patients included in this meta-analysis. Vitamin E was associated with a significant reduction in the incidence of prostate cancer (relative risk, 0.85; 95% CI, 0.73-0.96, number needed to treat=500), but it did not reduce the incidence of any other types of cancer.

CONCLUSIONS:

Vitamin E supplementation was not associated with a reduction in total mortality, cancer incidence, or cancer mortality, but it was associated with a statistically significant reduction in the incidence of prostate cancer. Vitamin E can be used in the prevention of prostate cancer in men who are at high risk of prostate cancer

VITAMINA D

Cancer Causes Control. 2003 Feb;14(1):1-12.

Calcium, vitamin D, dairy products, and risk of colorectal cancer in the Cancer Prevention Study II Nutrition Cohort (United States).

McCullough ML, Robertson AS, Rodriguez C, Jacobs EJ, Chao A, Carolyn J, Calle EE, Willett WC, Thun MJ.

Source

Epidemiology and Surveillance Research Department, American Cancer Society, 1599 Clifton Rd NE, Atlanta GA, 30309 USA.

Abstract

OBJECTIVE:

Calcium, vitamin D, and dairy product intake may reduce the risk of colorectal cancer. We therefore examined the association between these factors and risk of colorectal cancer in a large prospective cohort of United States men and women.

METHODS:

Participants in the Cancer Prevention Study II Nutrition Cohort completed a detailed questionnaire on diet, medical history, and lifestyle in 1992-93. After excluding participants with a history of cancer or incomplete dietary information, 60,866 men and 66,883 women remained for analysis. During follow-up through 31 August 1997 we documented 421 and 262 cases of incident colorectal cancers among men and women, respectively. Multivariate-adjusted rate ratios (RR) were calculated using Cox proportional hazards models.

RESULTS:

Total calcium intake (from diet and supplements) was associated with marginally lower colorectal cancer risk in men and women (RR = 0.87, 95% CI 0.67-1.12, highest vs lowest quintiles, p trend = 0.02). The association was strongest for calcium from supplements (RR = 0.69, 95% CI 0.49-0.96 for > or = 500 mg/day vs none). Total vitamin D intake (from diet and multivitamins) was also inversely associated with risk of colorectal cancer, particularly among men (RR = 0.71, 95% CI 0.51-0.98, p trend = 0.02). Dairy product intake was not related to overall risk.

CONCLUSIONS:

Our results support the hypothesis that calcium modestly reduces risk of colorectal cancer. Vitamin D was associated with reduced risk of colorectal cancer only in men

J Steroid Biochem Mol Biol. 2005 Oct;97(1-2):37-46. Epub 2005 Aug 1.

Vitamin D receptor agonists induce prostatic acid phosphatase to reduce cell growth and HER-2 signaling in LNCaP-derived human prostate cancer cells.

Stewart LV, Lyles B, Lin MF, Weigel NL.

Source

Department of Molecular and Cellular Biology, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030, USA.

Abstract

We have previously shown that concentrations of 1alpha,25-dihydroxyvitamin D(3) (1,25D) that induce G(0)/G(1) cell cycle arrest in androgen-dependent LNCaP prostate cancer cells also decrease expression of c-Myc, a proto-oncogene that stimulates progression from G(1) to S phase of the cell cycle. Since both c-Myc expression and cell cycle progression are regulated by tyrosine kinase activation, we examined the ability of 1,25D to alter tyrosine kinase signaling in LNCaP cells and the androgen-independent LNCaP C81 (C81 LN) cell line. 1,25D selectively reduced protein tyrosine phosphorylation within both the LNCaP and C81 LN cells. This reduction in tyrosine kinase signaling appears to result from elevated levels of cellular prostatic acid phosphatase (PAcP). Western blots and biochemical assays revealed 1,25D increases the level of active PAcP in both cell lines. In addition, 1,25D decreased tyrosine phosphorylation of HER-2, an EGFR family member inactivated by PAcP, and the HER-2 downstream adaptor protein p52 Shc in C81 LN cells. Inhibition of HER-2 signaling by AG825 reduces growth of C81 LN cells and the parental LNCaP cells. These data therefore suggest that 1,25D-mediated decreases in LNCaP and C81 LN cell growth are in part due to decreases in tyrosine kinase signaling that result from up-regulation of PAcP

Front Oncol. 2013 Sep 23;3:250.

Targeted Therapy for Breast Cancer Prevention.

den Hollander P, Savage MI, Brown PH.

Source

Department of Clinical Cancer Prevention, The University of Texas MD Anderson Cancer Center , Houston, TX , USA.

Abstract

With a better understanding of the etiology of breast cancer, molecularly targeted drugs have been developed and are being testing for the treatment and prevention of breast cancer. Targeted drugs that inhibit the estrogen receptor (ER) or estrogen-activated pathways include the selective ER modulators (tamoxifen, raloxifene, and lasofoxifene) and aromatase inhibitors (AIs) (anastrozole, letrozole, and exemestane) have been tested in preclinical and clinical studies. Tamoxifen and raloxifene have been shown to reduce the risk of breast cancer and promising results of AIs in breast cancer trials, suggest that AIs might be even more effective in the prevention of ER-positive breast cancer. However, these agents only prevent ER-positive breast cancer. Therefore, current research is focused on identifying preventive therapies for other forms of breast cancer such as human epidermal growth factor receptor 2 (HER2)-positive and triple-negative breast cancer (TNBC, breast cancer that does express ER,

progesterone receptor, or HER2). HER2-positive breast cancers are currently treated with anti-HER2 therapies including trastuzumab and lapatinib, and preclinical and clinical studies are now being conducted to test these drugs for the prevention of HER2-positive breast cancers. Several promising agents currently being tested in cancer prevention trials for the prevention of TNBC include poly(ADP-ribose) polymerase inhibitors, vitamin D, and rexinoids, both of which activate nuclear hormone receptors (the vitamin D and retinoid X receptors). This review discusses currently used breast cancer preventive drugs, and describes the progress of research striving to identify and develop more effective preventive agents for all forms of breast cancer

Anticancer Res. 2013 Sep;33(9):3861-6.

Vitamin d favorably alters the cancer promoting prostaglandin cascade.

Qin W, Smith C, Jensen M, Holick MF, Sauter ER.

Source

11937 U.S. Hwy 271, Tyler, TX, U.S.A. edward.sauter@uthct.edu.

Abstract

BACKGROUND:

Preclinical studies suggest that 1,25-dihydroxyvitamin D [1,25(OH)2D] and celecoxib inhibit prostaglandins (PGs) associated with cancer through different mechanisms. We determined if there was synergy in their use.

PATIENTS AND METHODS:

A total of 36 healthy women received daily for one month/menstrual cycle: placebo, 400 international units (IU) vitamin D-3, 2,000 IU vitamin D-3, or 2,000 IU vitamin D-3 plus 400 mg celecoxib. Serum and nipple aspirate fluid (NAF) were analyzed for PGE2 and transforming growth factor (TGF)β1 and -2; serum for 25(OH)D (total, -D-2, -D-3), plasma for celecoxib; and mammary duct RNA for cyclooxygenase (COX)2.

RESULTS:

25(OH)D-3 increased ($p<0.01$) only in the groups receiving 2,000 IU vitamin D-3. PGE2 decreased in the breast ($p=0.01$) only after receiving 2,000 IU vitamin D-3; 2,000 IU vitamin D-3 alone was more effective in decreasing PGE2 than 2,000 IU vitamin D-3 plus celecoxib ($p=0.018$). COX2 expression decreased only in the breasts of women taking 2,000 IU vitamin D-3. Change in circulating 25(OH)D-3 correlated with change in TGFβ2 in the breast.

CONCLUSION:

Vitamin D-3 reduces the PG cascade and increases TGFβ2 in a dose-dependent fashion. Adding celecoxib did not provide synergy

J Steroid Biochem Mol Biol. 2005 Oct;97(1-2):179-94. Epub 2005 Oct 19.

Vitamin D and prevention of colorectal cancer.

Gorham ED, Garland CF, Garland FC, Grant WB, Mohr SB, Lipkin M, Newmark HL, Giovannucci E, Wei M, Holick MF.

Source

Naval Health Research Center, San Diego, CA 92186, USA.

Abstract

BACKGROUND:

Inadequate photosynthesis or oral intake of Vitamin D are associated with high incidence rates of colorectal cancer, but the dose-response relationship has not been adequately studied.

METHODS:

Dose-response gradients from observational studies of Vitamin D intake and serum 25-hydroxyvitamin D were plotted as trend lines. The point on each linear trend line corresponding to an odds ratio of 0.50 provided the prediagnostic Vitamin D intake or 25-hydroxyvitamin D concentration associated with 50% lower risk compared to <100IU/day Vitamin D or <13ng/ml serum 25-hydroxyvitamin D. Medians of these values were determined.

RESULTS:

Overall, individuals with >or=1000IU/day oral Vitamin D ($p<0.0001$) or >or=33ng/ml (82nmol/l) serum 25-hydroxyvitamin D ($p<0.01$) had 50% lower incidence of colorectal cancer compared to reference values.

CONCLUSIONS:

Intake of 1000IU/day of Vitamin D, half the safe upper intake established by the National Academy of Sciences, was associated with 50% lower risk. Serum 25-hydroxyvitamin D of 33ng/ml, which is known to be safe, also was associated with 50% lower risk. Prompt public health action is needed to increase intake of Vitamin D(3) to 1000IU/day, and to raise 25-hydroxyvitamin D by encouraging a modest duration of sunlight exposure

Proc Soc Exp Biol Med. 1999 Jun;221(2):89-98.

Vitamin D and prostate cancer.

Blutt SE, Weigel NL.

Source

Department of Cell Biology, Baylor College of Medicine, Houston, Texas 77030, USA.

Abstract

Classically, the actions of vitamin D have been associated with bone and mineral metabolism. More recent studies have shown that vitamin D metabolites induce differentiation and/or inhibit cell proliferation of a number of malignant and nonmalignant cell types including prostate cancer cells. Epidemiological studies show correlations between the risk factors for prostate cancer and conditions that can result in decreased vitamin D levels. The active metabolite of vitamin D, 1,25-dihydroxyvitamin D3 (calcitriol), inhibits growth of both primary cultures of human prostate cancer cells and cancer cell lines, but the mechanism by which the cells are growth-inhibited has not been clearly defined. Initial studies suggest that calcitriol

alters cell cycle progression and may also initiate apoptosis. One of the disadvantages of using vitamin D in vivo is side-effects such as hypercalcemia at doses above physiological levels. Analogs of calcitriol have been developed that have comparable or more potent antiproliferative effects but are less calcemic. Further research into the mechanisms of vitamin D action in prostate and identification of suitable analogs for use in vivo may lead to its use in the treatment or prevention of prostate cancer

NIACINA / NADH

Mutat Res. 2001 Apr 18;475(1-2):45-56.

Niacin, poly(ADP-ribose) polymerase-1 and genomic stability.

Hageman GJ, Stierum RH.

Source

Department of Health Risk Analysis and Toxicology, University of Maastricht, 6200 MD, Maastricht, The Netherlands. ghageman@grat@unimaas.nl

Abstract

Nicotinic acid (NA) and nicotinamide (NAM), commonly called niacin, are the dietary precursors for NAD(+) (nicotinamide adenine dinucleotide), which is required for DNA synthesis, as well as for the activity of the enzyme poly(ADP-ribose) polymerase-1 (PARP-1; EC 2.4.2.30) for which NAD(+) is the sole substrate. The enzyme PARP-1 is highly activated by DNA strand breaks during the cellular genotoxic stress response, is involved in base excision repair, plays a role in p53 expression and activation, and hence, is thought to be important for genomic stability. In this review, first the absorption, metabolism of niacin to NAD(+), as well as the assessment of niacin status are discussed. Since NAD(+) is important for PARP-1 activity, various aspects of PARP-1 in relation to DNA synthesis and repair, and regulation of gene expression are addressed. This is followed by a discussion on interactions between dietary methyl donor deficiency, niacin status, PARP-1 activity and genomic stability. In vitro studies show that PARP-1 function is impaired and genomic stability decreased when cells are either depleted from NAD(+) or incubated with high concentrations of NAM which is a PARP-1 inhibitor. In vitro as well as animal studies indicate that niacin deficiency increases genomic instability especially in combination with genotoxic and oxidative stress. Niacin deficiency may also increase the risk for certain tumors. Preliminary data suggest that niacin supplementation may protect against UV-induced tumors of the skin in mice, but data on similar preventive effects in humans are not available. NAM has been shown in vitro to have an antioxidant activity comparable to that of ascorbic acid. Data on niacin status and genomic stability in vivo in humans are limited and yield ambiguous results. Therefore, no firm conclusions with respect to optimal niacin intake are possible. As a consequence of oral niacin supplementation, however, NAM levels in the body may increase, which may result in inhibition of PARP-1 and increased genomic instability. More studies are needed to define an optimal level of niacin nutriture in relation to genomic stability and tumorigenesis

J Clin Invest. 2013 Mar 1;123(3):1068-81. doi: 10.1172/JCI64264. Epub 2013 Feb 15.

Mitochondrial complex I activity and NAD+/NADH balance regulate breast cancer progression.

Santidrian AF, Matsuno-Yagi A, Ritland M, Seo BB, LeBoeuf SE, Gay LJ, Yagi T, Felding-Habermann B.

Source

Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, California 92037, USA.

Abstract

Despite advances in clinical therapy, metastasis remains the leading cause of death in breast cancer patients. Mutations in mitochondrial DNA, including those affecting complex I and oxidative phosphorylation, are found in breast tumors and could facilitate metastasis. This study identifies mitochondrial complex I as critical for defining an aggressive phenotype in breast cancer cells. Specific enhancement of mitochondrial complex I activity inhibited tumor growth and metastasis through regulation of the tumor cell NAD+/NADH redox balance, mTORC1 activity, and autophagy. Conversely, nonlethal reduction of NAD+ levels by interfering with nicotinamide phosphoribosyltransferase expression rendered tumor cells more aggressive and increased metastasis. The results translate into a new therapeutic strategy: enhancement of the NAD+/NADH balance through treatment with NAD+ precursors inhibited metastasis in xenograft models, increased animal survival, and strongly interfered with oncogene-driven breast cancer progression in the MMTV-PyMT mouse model. Thus, aberration in mitochondrial complex I NADH dehydrogenase activity can profoundly enhance the aggressiveness of human breast cancer cells, while therapeutic normalization of the NAD+/NADH balance can inhibit metastasis and prevent disease progression.

J Am Coll Nutr. 1993 Aug;12(4):412-6.

Niacin deficiency and cancer in women.

Jacobson EL.

Source

Dept. of Clinical Sciences, Markey Cancer Center, University of Kentucky, Lexington 40536-0080.

Abstract

A new interest in the relationship between niacin and cancer has evolved from the discovery that the principal form of this vitamin, NAD, is consumed as a substrate in ADP-ribose transfer reactions. Poly(ADP-ribose) polymerase, an enzyme activated by DNA strand breaks, is the ADP-ribosyltransferase of greatest interest with regard to effects on the niacin status of cells since its Km for NAD is high, and its activity can deplete NAD. Studies of the consequences of DNA damage in cultured mouse and human cells as a function of niacin status have supported the hypothesis that niacin may be a protective factor that limits carcinogenic events. To test this hypothesis in humans, we used a biochemical method based on the observation that as niacin nutriture decreases, NAD readily declines and NADP remains relatively constant. This has been demonstrated in both fibroblasts and in whole blood from humans. Thus, we use "niacin number," (NAD/NAD+NADP) x 100% from whole blood, as a measure of niacin status. Healthy control subjects showed a mean niacin number of 62.8 +/- 3.0 compared to 64.0 for individuals on a niacin-controlled diet. Analyses of women in the Malmö Diet and Cancer Study showed a mean niacin number of 60.4 with a range of 44 to 75. The distribution of niacin status in this population was nongaussian, with an unpredictably large number of individuals having low values.

Nutr Cancer. 2003;46(2):110-8.

Niacin and carcinogenesis.

Kirkland JB.

Source

Department of Human Biology and Nutritional Sciences, University of Guelph, Guelph, Ontario, Canada.

Abstract

The dietary status of niacin (vitamin B3) has the potential to influence DNA repair, genomic stability, and the immune system, eventually having an impact on cancer risk, as well as the side effects of chemotherapy in the cancer patient. In addition to its well-known redox functions in energy metabolism, niacin, in the form of NAD, participates in a wide variety of ADP-ribosylation reactions. Poly(ADP-ribose) is a negatively charged polymer synthesized, predominantly on nuclear proteins, by at least seven different enzymes. Poly(ADP-ribose) polymerase-1 (PARP-1) is responsible for the majority of polymer synthesis and plays important roles in DNA damage responses, including repair, maintenance of genomic stability, and signaling events for stress responses such as apoptosis. NAD is also used in the synthesis of mono(ADP-ribose), often on G proteins, with poorly understood roles in signal transduction. Last, NAD and NADP are required for the synthesis of cyclic ADP-ribose and nicotinic acid adenine dinucleotide (NAADP), two mediators of intracellular calcium signaling pathways. Disruption of any of these processes has the potential to impair genomic stability and deregulate cell division, leading to enhanced cancer risk. There are various sources of evidence that niacin status does have an impact on cancer risk, including animal models of leukemogenesis and skin cancer, as well as epidemiological data from human populations

TIAMINA

Cancer Genomics Proteomics. 2013 Jul-Aug;10(4):169-85.

The role of thiamine in cancer: possible genetic and cellular signaling mechanisms.

Lu'o'ng KV, Nguyn LT.

Source

FACP, FACE, FACN, FASN, FCCP, and FACAAI (SC), 14971 Brookhurst St. Westminster, CA 92683, U.S.A. lng2687765@aol.com.

Abstract

The relationship between supplemental vitamins and various types of cancer has been the focus of recent investigation, and supplemental vitamins have been reported to modulate cancer rates. A significant association has been demonstrated between cancer and low levels of thiamine in the serum. Genetic studies have helped identify a number of factors that link thiamine to cancer, including the solute carrier transporter (SLC19) gene, transketolase, transcription factor p53, poly(ADP-ribose) polymerase-1 gene, and the reduced form of nicotinamide adenine dinucleotide phosphate. Thiamine supplementation may contribute to a high rate of tumor cell survival, proliferation and chemotherapy resistance. Thiamine has also been implicated in cancer through its effects on matrix metalloproteinases, prostaglandins, cyclooxygenase-2, reactive oxygen species, and nitric oxide synthase. However, some studies have suggested that thiamine may exhibit some antitumor effects. The role of thiamine in cancer is controversial. However, thiamine deficiency may occur in patients with cancer and cause serious disorders, including Wernicke's encephalopathy, that require parenteral thiamine supplementation. A very high dose of thiamine produces a growth-inhibitory effect in cancer. Therefore, further investigations of thiamine in cancer are needed to clarify this relationship

Eur J Biochem. 2001 Aug;268(15):4177-82.

The effect of thiamine supplementation on tumour proliferation. A metabolic control analysis study.

Comín-Anduix B, Boren J, Martinez S, Moro C, Centelles JJ, Trebukhina R, Petushok N, Lee WN, Boros LG, Cascante M.

Source

Department of Biochemistry and Molecular Biology, IDIBAPS, University of Barcelona, Spain.

Abstract

Thiamine deficiency frequently occurs in patients with advanced cancer and therefore thiamine supplementation is used as nutritional support. Thiamine (vitamin B1) is metabolized to thiamine pyrophosphate, the cofactor of transketolase, which is involved in ribose

synthesis, necessary for cell replication. Thus, it is important to determine whether the benefits of thiamine supplementation outweigh the risks of tumor proliferation. Using oxythiamine (an irreversible inhibitor of transketolase) and metabolic control analysis (MCA) methods, we measured an in vivo tumour growth control coefficient of 0.9 for the thiamine-transketolase complex in mice with Ehrlich's ascites tumour. Thus, transketolase enzyme and thiamine clearly determine cell proliferation in the Ehrlich's ascites tumour model. This high control coefficient allows us to predict that in advanced tumours, which are commonly thiamine deficient, supplementation of thiamine could significantly increase tumour growth through transketolase activation. The effect of thiamine supplementation on tumour proliferation was demonstrated by in vivo experiments in mice with the ascites tumour. Thiamine supplementation in doses between 12.5 and 250 times the recommended dietary allowance (RDA) for mice were administered starting on day four of tumour inoculation. We observed a high stimulatory effect on tumour growth of 164% compared to controls at a thiamine dose of 25 times the RDA. This growth stimulatory effect was predicted on the basis of correction of the pre-existing level of thiamine deficiency (42%), as assayed by the cofactor/enzyme ratio. Interestingly, at very high overdoses of thiamine, approximately 2500 times the RDA, thiamine supplementation had the opposite effect and caused 10% inhibition of tumour growth. This effect was heightened, resulting in a 36% decrease, when thiamine supplementation was administered from the 7th day prior to tumour inoculation. Our results show that thiamine supplementation sufficient to correct existing thiamine deficiency stimulates tumour proliferation as predicted by MCA. The tumour inhibitory effect at high doses of thiamine is unexplained and merits further study.

Anticancer Res. 1998 Jan-Feb;18(1B):595-602.

Thiamine supplementation to cancer patients: a double edged sword.

Boros LG, Brandes JL, Lee WN, Cascante M, Puigjaner J, Revesz E, Bray TM, Schirmer WJ, Melvin WS.

Source

Ohio State University College of Medicine, Department of Surgery, Columbus 43210, USA. lboros@magnus.acs.ohio-state.edu

Abstract

The objectives of this review are to (a) explain the mechanism by which thiamine (vitamin B1) promotes nucleic acid ribose synthesis and tumor cell proliferation via the nonoxidative transketolase (TK) pathway; (b) estimate the thiamine intake of cancer patients and (c) provide background information and to develop guidelines for alternative treatments with antithiamine transketolase inhibitors in the clinical setting. Clinical and experimental data demonstrate increased thiamine utilization of human tumors and its interference with experimental chemotherapy. Analysis of RNA ribose indicates that glucose carbons contribute to over 90% of ribose synthesis in cultured cervix und pancreatic carcinoma cells and that ribose is synthesized primarily through the thiamine dependent TK pathway (> 70%). Antithiamine compounds significantly inhibit nucleic acid synthesis and tumor cell proliferation in vitro and in vivo in several tumor models. The medical literature reveals little information regarding the role of the thiamine dependent TK reaction in tumor cell ribose production which is a central process in de novo nucleic acid synthesis and the salvage pathways for purines. Consequently, current thiamine administration protocols oversupply thiamine by 200% to 20,000% of the recommended dietary allowance, because it is considered harmless

and needed by cancer patients. The thiamine dependent TK pathway is the central avenue which supplies ribose phosphate for nucleic acids in tumors and excessive thiamine supplementation maybe responsible for failed therapeutic attempts to terminate cancer cell proliferation. Limited administration of thiamine and concomitant treatment with transketolase inhibitors is a more rational approach to treat cancer.

FOLATOS

J Natl Cancer Inst. 1995 Feb 15;87(4):265-73.

Alcohol, low-methionine--low-folate diets, and risk of colon cancer in men.

Giovannucci E, Rimm EB, Ascherio A, Stampfer MJ, Colditz GA, Willett WC.

Source

Channing Laboratory, Department of Medicine, Harvard Medical School, Boston, Mass., USA.

Abstract

BACKGROUND:

Methylation of DNA, which may have a role in the regulation of gene expression, depends on dietary folate and methionine. Because aberrant DNA methylation may contribute to the initiation or progression of colon cancer, we hypothesized that deficient intakes of folate or methionine and high consumption of alcohol, an antagonist of methyl-group metabolism, increase risk of colon neoplasia. Previously, a high-alcohol and low-methionine--low-folate (methyl-deficient) diet was shown to be related to a higher risk of colon adenomas, precursors of cancer.

PURPOSE:

Our goal was to determine if ingestion of a high-alcohol, methyl-deficient diet is related directly to risk of colon cancer.

METHODS:

We assessed dietary intake for a 1-year period for a cohort of 47,931 U.S. male health professionals, 40-75 years old and free of diagnosed cancer in 1986. We assessed diet by using a validated, semiquantitative food-frequency questionnaire. During 6 years of follow-up, we documented 205 new cases of colon cancer in this cohort.

RESULTS:

Current alcohol intake was directly related to risk of colon cancer (multivariate relative risk [RR] = 2.07; 95% confidence interval [CI] = 1.29-3.32, for > 2 drinks versus < or = 0.25 drink daily; P trend = .005), and past drinkers were also at higher risk (RR = 1.95; 95% CI = 1.22-3.10). Individually, folate and methionine intakes were weakly inversely associated with risk of colon cancer. An adverse effect of a high-alcohol, low-methyl diet was not observed among regular users of aspirin, who have previously been shown to be at lower risk for colon cancer. Combinations of high alcohol and low methionine and folate intakes yielded striking associations for total colon cancer (RR = 3.30 [95% CI = 1.58-6.88] comparing high-methyl diets with low-methyl diets among nonusers of aspirin) and for cancers of the distal colon (RR = 7.44; 95% CI = 1.72-32.1). Among men with high intakes of folate or methionine, alcohol levels of > 2 drinks daily were not associated with risk of colon cancer. The increased risk of colon cancer associated with alcohol and methyl-deficient diets was not confounded by smoking; intakes of fat, red meat, and fiber; level of physical activity; multivitamin or aspirin use; and body mass index.

CONCLUSIONS:

These findings support the hypothesis that substantial consumption of alcohol, when combined with inadequate intakes of folate and methionine, may increase risk of colon cancer and confirm similar findings in adenomas.

IMPLICATIONS:

These data provide further support of recommendations to avoid excess alcohol consumption and to increase dietary folate to lower the risk of colon cancer

Genet Mol Res. 2011 Dec 14;10(4):3738-46. doi: 10.4238/2011.December.14.8.

Methylenetetrahydrofolate reductase genotypes and haplotypes associated with susceptibility to colorectal cancer in an eastern Chinese Han population.

Li H, Xu WL, Shen HL, Chen QY, Hui LL, Long LL, Zhu XL.

Source

Department of Central Laboratory, The Affiliated People's Hospital, Jiangsu University, Zhenjiang, Jiangsu, China.

Abstract

Methylenetetrahydrofolate reductase (MTHFR) plays an important role in folate metabolism and is involved in DNA synthesis, DNA repair and DNA methylation. The two common functional polymorphisms of MTHFR, C677T and A1298C have been associated with several diseases, including cancer. We made a case-control study to analyze a possible association of MTHFR gene polymorphisms C677T and A1298C with risk for colorectal cancer in an eastern Chinese Han population of 137 patients with a confirmed histopathological diagnosis of CRC and 145 age- and gender-matched controls with no history of cancer. DNA was isolated from peripheral blood samples and the genotypes were determined by PCR-RFLP. The concentrations of folate in plasma were measured by chemiluminescence immunoassay. The MTHFR 677TT genotype had a protective effect against colorectal cancer, with an odds ratio (OR) = 0.467 (95% confidence interval (CI) = 0.225-0.966). The 1298CC genotype was significantly correlated with a reduced risk of colorectal cancer (OR = 0.192; 95%CI = 0.040-0.916). Compared with the MTHFR 677CC and MTHFR 1298 AA genotypes, for individuals who carried both MTHFR 677CC and 1298CC genotypes, the OR of colorectal cancer was 0.103 (95%CI = 0.012-0.900); among individuals who carried both MTHFR 677TT and 1298AC genotypes, the OR for risk of colorectal cancer was 0.169 (95%CI = 0.044-0.654). MTHFR 677TT+CT genotypes had a significantly lower plasma folate concentration than those with the MTHFR 677CC genotype. MTHFR 1298AC+CC genotypes had a lower plasma folate concentration than those with the MTHFR 1298AA genotype ($P < 0.05$). In conclusion, subjects with the MTHFR 677TT and MTHFR 1298CC genotypes appeared to have a significantly lower risk for colorectal cancer. MTHFR haplotypes 677CC/1298CC and 677TT/1298AC were less common in cases than in controls. These haplotypes, when compared to the most common haplotype 677CC/1298AA, were associated with a decreased risk for colorectal cancer. We conclude that plasma folate level is influenced by MTHFR genotypes.

Cancer Sci. 2005 Sep;96(9):535-42.

Genetic polymorphisms of methylenetetrahydrofolate reductase and colorectal cancer and adenoma.

Kono S, Chen K.

Source

Department of Preventive Medicine, Faculty of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Fukuoka 812-8582, Japan. skono@phealth.med.kyushu-u.ac.jp

Abstract

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme regulating folate metabolism, which affects DNA methylation and synthesis. Two functional, common polymorphisms (C677T and A1298C) are known in the MTHFR gene. MTHFR activity is lowered in individuals with the 677TT genotype and is somewhat reduced in those with the 1298CC genotype. We reviewed the consistency of reported associations of these polymorphisms with colorectal cancer and adenoma with consideration of the effects of nutritional status. A total of 16 studies have addressed the association between MTHFR C677T polymorphism and colorectal cancer in 10 countries. Decreased risk of colorectal cancer associated with the 677TT genotype has fairly consistently been observed, with few exceptions. This decrease was observable in people with either high or low folate status. Alteration in the thymidylate pool associated with MTHFR activity is postulated as an underlying mechanism. Studies on the A1298C polymorphism are limited, and their results are variable. Almost all of seven studies of colorectal adenoma have found no association between C677T polymorphism and adenoma, but the 677TT genotype seems to be related to increased risk when folate status is poor. Reduced availability of methyl groups for DNA methylation might be more relevant to adenoma formation. Although the underlying mechanisms still remain to be clarified, epidemiological findings regarding MTHFR C677T polymorphism provide strong evidence that adequate folate status confers protection from colorectal cancer

Mutat Res. 2007 Sep 1;622(1-2):14-8. Epub 2007 May 21.

The interactive effect of methyl-group diet and polymorphism of methylenetetrahydrofolate reductase on the risk of colorectal cancer.

Kim DH.

Source

Department of Social and Preventive Medicine, Hallym University College of Medicine, 1 Okchon-dong, Chunchon, Kangwon-do 200-702, South Korea. dhkims@hallym.ac.kr

Abstract

Higher intakes of vegetables have been reported to be associated with a reduced risk of colorectal cancer. Folate, a water-soluble B vitamin, and one of the major micronutrients in vegetables, may be partly responsible for this beneficial effect. Conversely, a high alcohol intake has been related to an increased risk of colorectal cancer. The combination of high folate and low alcohol intake, "methyl group diets", was reported to have a strong protective effect. These findings support a role of methyl group availability as an underlying mechanism for an effect of folate on colorectal carcinogenesis. The protective effect of the homozygous

variant TT form of the MTHFR genotype (C677T) on the risk of colorectal cancer seems to be modified by the level of methyl diets, that is, by folate, which has a protective effect, or conversely by alcohol. Recommendation of higher intake of folate and lower intake of alcohol to the target population, especially those with TT genotype of MTHFR, may be an effective preventive approach against colorectal cancer

Public Health. 2013 Jul;127(7):607-13. doi: 10.1016/j.puhe.2013.04.008. Epub 2013 Jun 14.

Folate intake and pancreatic cancer risk: an overall and dose-response meta-analysis.

Lin HL, An QZ, Wang QZ, Liu CX.

Source

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Abstract

OBJECTIVE:

Inconsistent findings of association between supplemental folate consumption and pancreatic cancer risk have been observed in the literature. This study aims to summarize the relationship between folate intake and risk of pancreatic cancer.

STUDY DESIGN:

Pertinent studies published before November 2011 were identified by searching PubMed and Embase and by reviewing the reference lists of retrieved articles. The summary relative risks were estimated by the random effects model. A linear regression analysis of the natural logarithm of the relative risk (RR) was carried out to assess a possible dose-response relationship between folate intake and pancreatic cancer risk.

RESULTS:

Ten studies on dietary and supplemental folate intake and pancreatic cancer (4 case-control and 6 cohort studies) were included in the meta-analysis. The pooled RRs of pancreatic cancer for the highest vs lowest categories of dietary folate intake and supplemental folate intake were 0.66 (95% CI: 0.49-0.88) and 1.08 (95% CI, 0.82-1.41), respectively. The dose-response meta-analysis indicated that a 100 μg/day increment in dietary folate intake conferred a RR of 0.93 (95% CI: 0.90-0.97). These findings support the hypothesis that dietary folate may play a protective role in carcinogenesis of pancreatic cancer.

ÁCIDO ALFA LIPOICO

Nutr Hosp. 2013 Julio-Agosto;28(4):1031-1038.

[ALPHA LIPOIC ACID AND ITS ANTIOXIDANT AGAINST CANCER AND DISEASES OF CENTRAL SENSITIZATION.]

[Article in Spanish]
Durand M, Mach N.

Abstract

Introduction: The alpha lipoic acid (ALA) may control and limit the production of free radicals, influencing the development of pathologies such cancer or central sensitization diseases. However, the molecular mechanisms are still not elucidated. Objective: The objective of the present review is to contrast the antioxidant properties of ALA in the prevention and development of pathologies related to the oxidative stress. Materials and methods: In this work, more than 100 articles published during the last 20 years that relate ALA consumption and pathologies related to the oxidative stress have been analysed. The articles have been obtained from different specialized databases (PubMed central, Web of science, Elsevier Journal, Science Direct) and included experiments in animals, cells, and humans. Domains evaluated included ALA, central sensitization diseases, free radicals, and ALA. Results and discussion: Results from in vitro and laboratory animals experiments demonstrate that ALA controls the cell apoptosis of different type of cancers through out the increase of reactive oxygen species, and decrease of cell growth. Moreover, results demonstrated that ALA presents an antioxidant capacity and the ability to regenerate other antioxidants, which is essential to treat the central sensitization diseases. Conclusions: The ALA plays a significant role as antioxidant and prooxidant in cancer and central sensitization diseases, although more extensive studies are required to determine the clinical significance in humans

Anticancer Drugs. 2013 Jul;24(6):555-65. doi: 10.1097/CAD.0b013e32836181eb.

α-Lipoic acid prevents p53 degradation in colon cancer cells by blocking NF-κB induction of RPS6KA4.

Yoo TH, Lee JH, Chun HS, Chi SG.

Source

Department of Life Sciences, School of Life Sciences and Biotechnology, Korea University, Seoul, Republic of Korea.

Abstract

α-Lipoic acid (α-LA) is a biogenic antioxidant that has been used successfully in the treatment of diabetic polyneuropathy and its application to many oxidative stress-associated chronic diseases has increased. In this study, we investigated the effect of α-LA on colorectal cancer cell growth and its underlying mechanism. α-LA treatment resulted in a marked reduction in

the growth of HCT116 colon cancer cells in a dose-dependent manner through the G1 arrest of the cell cycle and apoptosis induction. α-LA treatment significantly increased tumor cell response to various apoptotic stresses, such as etoposide, 5-fluorouracil, UVC, γ-irradiation, hypoxia, and tumor necrosis factor α (TNFα). Interestingly, α-LA increased p53 protein stability and its apoptosis-enhancing effect was more evident in wild-type p53-carrying cells compared with p53-deficient cells, suggesting that the proapoptotic role of α-LA is associated with its p53-stabilizing function. On the basis of our microarray data showing α-LA downregulation of the ribosomal protein p90S6K (RPS6KA4), which has been reported to inhibit p53 function, we tested whether α-LA regulation of RPS6KA4 is associated with its proapoptotic function. α-LA treatment led to a marked reduction in the RPS6KA4 mRNA level in multiple colorectal cancer cells and restoration of RPS6KA4 expression markedly attenuated α-LA induction of apoptosis in a p53-dependent manner. In addition, we observed that RPS6KA4 expression is activated by TNFα whereas both basal and TNFα induction of RPS6KA4 are inhibited by the nuclear factor-κB (NF-κB) inhibitor BAY11-7082 or transfection of a dominant-negative mutant of NF-κB, indicating that NF-κB plays a crucial role in RPS6KA4 gene expression. Finally, we found that α-LA exerts an inhibitory effect on the nuclear translocation of NF-κB triggered by TNFα. Collectively, our study shows that α-LA suppresses colorectal tumor cell growth at least partially by preventing RPS6KA4-mediated p53 inhibition through blockade of NF-κB signaling.

Pharmacol Rep. 2011;63(4):849-58.

Lipoic acid - biological activity and therapeutic potential.

Gorąca A, Huk-Kolega H, Piechota A, Kleniewska P, Ciejka E, Skibska B.

Source

Department of Cardiovascular Physiology, Medical University of Lodz, Mazowiecka 6/8, PL 92-215 Łódź, Poland.

Abstract

α-Lipoic acid (LA; 5-(1,2-dithiolan-3-yl)pentanoic acid) was originally isolated from bovine liver by Reed et al. in 1951. LA was once considered a vitamin. Subsequently, it was found that LA is not a vitamin and is synthesized by plants and animals. LA is covalently bound to the ε-amino group of lysine residues and functions as a cofactor for mitochondrial enzymes by catalyzing the oxidative decarboxylation of pyruvate, α-ketoglutarate and branched-chain α-keto acids. LA and its reduced form - dihydrolipoic acid (DHLA), meet all the criteria for an ideal antioxidant because they can easily quench radicals, can chelate metals, have an amphiphlic character and they do not exhibit any serious side effects. They interact with other antioxidants and can regenerate them. For this reason, LA is called an antioxidant of antioxidants. LA has an influence on the second messenger nuclear factor κB (NF-κB) and attenuates the release of free radicals and cytotoxic cytokines. The therapeutic action of LA is based on its antioxidant properties. Current studies support its use in the ancillary treatment of many diseases, such as diabetes, cardiovascular, neurodegenerative, autoimmune diseases, cancer and AIDS. This review was undertaken to gather the most recent information regarding the therapeutic properties of LA and its possible utility in disease treatment.

COENZIMA Q10

Medsurg Nurs. 2012 Nov-Dec;21(6):367-71.

Coenzyme Q10--a therapeutic agent.

Lance J, McCabe S, Clancy RL, Pierce J.

Source

Naval Medical Center, Portsmouth, VA, USA.

Abstract

Coenzyme Q10 (CoQ10) is critical to production of adenosine triphosphate and is an antioxidant that scavenges reactive oxygen species during oxidative stress. The use of CoQ10 in treating oxidative stress in cardiovascular diseases, diabetes, and cancer is reviewed.

Asian Pac J Cancer Prev. 2011;12(6):1399-403.

Lipid peroxidation, DNA damage and coenzyme Q10 in lung cancer patients--markers for risk assessment?

Cobanoglu U, Demir H, Cebi A, Sayir F, Alp HH, Akan Z, Gur T, Bakan E.

Source

Department of Thoracic Surgery, Divison of Biochemistry, Faculty of Medicine, Yuzuncu Yil University, Van, Turkey.

Abstract

OBJECTIVES:

Early diagnosis and prevention is very important for lung cancer patients. Previous studies have emphasized that the level of coenzyme Q10 (CoQ10), present primarily in mitochondria, decreases with age and is low in patients with chronic diseases. Our goal was to find out if there is any relationship between lung cancer and CoQ10 and lipid peroxidation levels.

DESIGN AND METHODS:

Blood samples from lung cancer patients were collected. Total and oxide CoQ10 levels, 8-OHdG (product of DNA damage), and malondialdehyde (MDA) levels (lipid peroxidation) were analyzed with high performance liquid chromatography (HPLC).

RESULTS:

The MDA level ($P<0.001$) and DNA damage rate (8-OHdG) ($P<0.001$) was higher in cancer patients than in the control group; in contrast, theCoQ10 enzyme level was significantly lower ($P<0.001$).

CONCLUSION:

The results suggest that the aforementioned parameters can be useful for lung cancer risk assessment

Altern Ther Health Med. 2013 Aug 15. pii: at5027.

Mitochondrial Dysfunction and Chronic Disease: Treatment With Natural Supplements.

Nicolson GL.

Abstract

Loss of function in mitochondria, the key organelle responsible for cellular energy production, can result in the excess fatigue and other symptoms that are common complaints in almost every chronic disease. At the molecular level, a reduction in mitochondrial function occurs as a result of the following changes: (1) a loss of maintenance of the electrical and chemical transmembrane potential of the inner mitochondrial membrane, (2) alterations in the function of the electron transport chain, or (3) a reduction in the transport of critical metabolites into mitochondria. In turn, these changes result in a reduced efficiency of oxidative phosphorylation and a reduction in production of adenosine-5'-triphosphate (ATP). Several components of this system require routine replacement, and this need can be facilitated with natural supplements. Clinical trials have shown the utility of using oral replacement supplements, such **as L-carnitine, alpha-lipoic acid (α-lipoic acid [1,2-dithiolane-3-pentanoic acid]), coenzyme Q10 (CoQ10 [ubiquinone]), NADH** (reduced nicotinamide adenine dinucleotide), membrane phospholipids, and other supplements. Combinations of these supplements can reduce significantly the fatigue and other symptoms associated with chronic disease and can naturally restore mitochondrial function, even in long-term patients with intractable fatigue

Cancer Epidemiol Biomarkers Prev. 2011 Apr;20(4):708-10. doi: 10.1158/1055-9965.EPI-10-1309. Epub 2011 Feb 4.

Plasma coenzyme Q10 levels and prostate cancer risk: the multiethnic cohort study.

Chai W, Cooney RV, Franke AA, Caberto CP, Wilkens LR, Le Marchand L, Goodman MT, Henderson BE, Kolonel LN.

Source

Epidemiology Program, University of Hawaii Cancer Center, 1236 Lauhala Street, Honolulu, HI 96813, USA.

Abstract

BACKGROUND:

Coenzyme Q10 (CoQ10) is considered to be a potential anticancer agent, but epidemiologic evidence regarding CoQ10 and prostate cancer risk is lacking. We examined the association of circulating CoQ10 levels with prostate cancer risk, using prediagnostic blood samples.

METHODS:

Each of the 307 cases was individually matched to approximately 2 controls, for a total of 596 controls, on age, ethnicity, geographic location, date/time of specimen collection, and hours of fasting. Logistic regression was used to compute ORs and 95% CIs.

RESULTS:

There was no overall statistically significant association of plasma CoQ10 levels with prostate cancer risk (P(trend) = 0.50). However, after matched sets in which controls who had possible undiagnosed prostate cancer (prostate specific antigen value >4.0) were excluded, the ORs for quintiles 2 to 5 were all less than 1.0.

CONCLUSIONS:

The results suggest the possibility that moderate levels of circulating CoQ10 may be optimal for the reduction of prostate cancer risk; however, the findings were weak and not statistically significant. Because this is the first epidemiologic study of the association between CoQ10 and prostate cancer, further research on this topic is needed.

IMPACT:

If a nutritional factor such as CoQ10 were determined to reduce prostate cancer risk, it would have considerable public health significance because of the very high incidence of this cancer

Asian Pac J Cancer Prev. 2011;12(6):1399-403.

Lipid peroxidation, DNA damage and coenzyme Q10 in lung cancer patients--markers for risk assessment?

Cobanoglu U, Demir H, Cebi A, Sayir F, Alp HH, Akan Z, Gur T, Bakan E.

Source

Department of Thoracic Surgery, Divison of Biochemistry, Faculty of Medicine, Yuzuncu Yil University, Van, Turkey.

Abstract

OBJECTIVES:

Early diagnosis and prevention is very important for lung cancer patients. Previous studies have emphasized that the level of coenzyme Q10 (CoQ10), present primarily in mitochondria, decreases with age and is low in patients with chronic diseases. Our goal was to find out if there is any relationship between lung cancer and CoQ10 and lipid peroxidation levels.

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Blood samples from lung cancer patients were collected. Total and oxide CoQ10 levels, 8-OHdG (product of DNA damage), and malondialdehyde (MDA) levels (lipid peroxidation) were analyzed with high performance liquid chromatography (HPLC).

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The MDA level (P<0.001) and DNA damage rate (8-OHdG) (P<0.001) was higher in cancer patients than in the control group; in contrast, theCoQ10 enzyme level was significantly lower (P<0.001).

CONCLUSION:

The results suggest that the aforementioned parameters can be useful for lung cancer risk assessment

VITAMINA B12

Mutat Res. 1999 Jul 16;428(1-2):299-304.

Micronucleus frequency in human lymphocytes is related to plasma vitamin B12 and homocysteine.

Fenech M.

Source

CSIRO Human Nutrition, PO Box 10041 Gouger Street, Adelaide, Australia. michael.fenech@dhn.csiro.au

Abstract

In a series of studies, we have been able to confirm that the micronucleus index in cytokinesis-blocked lymphocytes is significantly negatively correlated with plasma vitamin B12 (B12) concentration and significantly positively correlated with plasma homocysteine (HC). Furthermore we have shown in a randomised double-blind placebo-controlled dietary intervention study that intake of 3.5 times the RDI of folic acid and B12 significantly reduces the micronucleus index only in those with above average levels of micronucleus frequency. Micronucleus frequency is minimised when plasma HC is below 7.5 micromol/l and plasma B12 is above 300 pmol/l. Therefore, it is important to take account of the effect of B12 and HC when using the micronucleus assay for human biomonitoring studies.

Mutat Res. 2001 Apr 18;475(1-2):57-67.

The role of folic acid and Vitamin B12 in genomic stability of human cells.

Fenech M.

Source

CSIRO Health Sciences and Nutrition, Adelaide, Australia. michael.fenech@hsn.csiro.au

Abstract

Folic acid plays a critical role in the prevention of chromosome breakage and hypomethylation of DNA. This activity is compromised when Vitamin B12 (B12) concentration is low because methionine synthase activity is reduced, lowering the concentration of S-adenosyl methionine (SAM) which in turn may diminish DNA methylation and cause folate to become unavailable for the conversion of dUMP to dTMP. The most plausible explanation for the chromosome-breaking effect of low folate is excessive uracil misincorporation into DNA, a mutagenic lesion that leads to strand breaks in DNA during repair. Both in vitro and in vivo studies with human cells clearly show that folate deficiency causes expression of chromosomal fragile sites, chromosome breaks, excessive uracil in DNA, micronucleus formation and DNA hypomethylation. In vivo studies show that Vitamin B12 deficiency and elevated plasma homocysteine are significantly correlated with increased micronucleus formation. In vitro experiments indicate that genomic instability in human cells is minimised when folic acid concentration in culture medium is >227nmol/l. Intervention studies in humans show: (a) that DNA hypomethylation, chromosome breaks, uracil misincorporation and micronucleus formation are minimised when red cell folate concentration is >700nmol/l folate; and (b) micronucleus formation is minimised when plasma concentration of Vitamin B12 is >300pmol/l and plasma homocysteine is <7.5micromol/l. These concentrations are achievable at intake levels in excess of current RDIs i.e. more than 200-

400microgram folic acid per day and more than 2microgram Vitamin B12 per day. A placebo-controlled study with a dose-response suggests that based on the micronucleus index in lymphocytes, an RDI level of 700microgram/day for folic acid and 7microgram/day for Vitamin B12 would be appropriate for genomic stability in young adults. Dietary intakes above the current RDI may be particularly important in those with extreme defects in the absorption and metabolism of these Vitamins, for which ageing is a contributing factor.

SELENIO

J Natl Cancer Inst. 1998 Aug 19;90(16):1219-24.

Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer.

Yoshizawa K, Willett WC, Morris SJ, Stampfer MJ, Spiegelman D, Rimm EB, Giovannucci E.

Source

Department of Nutrition, Harvard School of Public Health, Boston, MA, USA.

Abstract

BACKGROUND:

In a recent randomized intervention trial, the risk of prostate cancer for men receiving a daily supplement of 200 microg selenium was one third of that for men receiving placebo. By use of a nested case-control design within a prospective study, i.e., the Health Professionals Follow-Up Study, we investigated the association between risk of prostate cancer and prediagnostic level of selenium in toenails, a measure of long-term selenium intake.

METHODS:

In 1986, 51,529 male health professionals aged 40-75 years responded to a mailed questionnaire to form the prospective study. In 1987, 33,737 cohort members provided toenail clippings. In 1988, 1990, 1992, and 1994, follow-up questionnaires were mailed. From 1989 through 1994, 181 new cases of advanced prostate cancer were reported. Case and control subjects were matched by age, smoking status, and month of toenail return. Selenium levels were determined by neutron activation. All P values are two-sided.

RESULTS:

The selenium level in toenails varied substantially among men, with quintile medians ranging from 0.66 to 1.14 microg/g for control subjects. When matched case-control data were analyzed, higher selenium levels were associated with a reduced risk of advanced prostate cancer (odds ratio [OR] for comparison of highest to lowest quintile = 0.49; 95% confidence interval [CI] = 0.25-0.96; P for trend = .11). After additionally controlling for family history of prostate cancer, body mass index, calcium intake, lycopene intake, saturated fat intake, vasectomy, and geographical region, the OR was 0.35 (95% CI = 0.16-0.78; P for trend = .03).

CONCLUSIONS:

Our results support earlier findings that higher selenium intakes may reduce the risk of prostate cancer. Further prospective studies and randomized trials of this relationship should be conducted.

Mol Cell Biochem. 2013 Sep 20. [Epub ahead of print]

Combination of sulfamethoxazole and selenium in anticancer therapy: a novel approach.

Gupta R, Kazmi I, Afzal M, Khan R, Chauhan M, Al-Abbasi FA, Ahmad A, Anwar F.

Source

Siddhartha Institute of Pharmacy, Dobachi, Near IT Park, Dehra Dun, 248001, Uttarakhand, India.

Abstract

Sulfonamides have been reported to possess substantial antitumor activity as they act as carbonic anhydrase inhibitors. In addition, selenium appears to have a protective effect at various stages of cancer due to its antioxidant property, enhanced carcinogen detoxification, inhibition of cell invasion, and by inhibiting angiogenesis. Here, in the present study we aimed to evaluate and synergize the cytotoxic activity of sulfonamide and selenium (SM+SE) as effective therapy in the treatment of DENA-induced HCC. Hepatocarcinogeneis was induced by a single intraperitoneal injection of diethylnitrosamine (DENA) (200 mg/kg) in phosphate buffer. 30 Male Wistar rats used in this study were divided randomly into five equal groups ($n = 6$). DENA-administered animals showed significant alteration ($p < 0.001$) in liver-specific enzymes-glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (ALP), and Alpha fetoproteins (AFP), and also induced severe histopathological changes in the hepatic tissues. Interestingly, treatment with (SE+SE) (SM 30 mg/kg + SE 3 mg/kg) significantly reduced ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$) the elevated AFP, SGOT, SGPT, and ALP levels, respectively, suggesting that combination therapy of SM+SE has a potential to treat DENA-induced liver damage

Chem Soc Rev. 2013 Sep 13.

Which form is that? The importance of selenium speciation and metabolism in the prevention and treatment of disease.

Weekley CM, Harris HH.

Source

School of Chemistry and Physics, The University of Adelaide, SA 5005, Australia. claire.weekley@adelaide.edu.au.

Abstract

The biological activity of selenium is dependent upon its speciation. We aim to integrate selenium speciation and metabolism into a discussion of the mechanisms by which selenium exerts its biological activity. First, we present the current status of selenium in the prevention of cancer, cardiovascular and neurodegenerative diseases with particular attention paid to the results of major chemoprevention trials involving selenium supplementation. A comprehensive review of the current understanding of the metabolism of common dietary selenium compounds - selenite, selenomethionine, methylselenocysteine and selenocystine - is presented, with discussion of the evidence for the various metabolic pathways and their products. The antioxidant, prooxidant and other mechanisms of the dietary selenium compounds have been linked to their disease prevention and treatment properties. The evidence for these various mechanisms - in vitro, in cells and in vivo - is evaluated with emphasis on the selenium metabolites involved. We conclude that dietary selenium compounds should be considered prodrugs, whose biological activity will depend on the activity of the various metabolic pathways in, and the redox status of, cells and tissues. These factors should be considered in future laboratory research and in selecting selenium compounds for trials of disease prevention and treatment by selenium supplementation

Pharmacol Ther. 1998 Sep;79(3):179-92.

Chemopreventive agents: selenium.

Combs GF Jr, Gray WP.

Source

Division of Nutritional Sciences, Cornell University, Ithaca, NY 14853, USA.

Abstract

The element selenium (Se) was recognized only 40 years ago as being essential in the nutrition of animals and humans. It is recognized as being an essential component of a number of enzymes, in which it is present as the amino acid selenocysteine. Se compounds have also been found to inhibit tumorigenesis in a variety of animal models, and recent studies indicate that supplemental Se in human diets may reduce cancer risk. The antitumorigenic activities have been associated with Se intakes that correct nutritionally deficient status in animals, as well as higher intakes that are substantially greater than those associated with maximal expression of the selenocysteine-containing enzymes. Therefore, it is proposed that while some cancer protection, particularly that involving antioxidant protection, involves selenoenzymes, specific Se metabolites, which are produced in significant amounts at relatively high Se intakes, also discharge antitumorigenic functions. According to this two-stage model of the roles of Se in cancer prevention, individuals with nutritionally adequate Se intakes may benefit from Se supplementation. Evidence for chemoprevention by Se and for the apparent mechanisms underlying these effects is reviewed to the end of facilitating the development of the potential of Se compounds as cancer chemopreventive agents

ZINC

Nutr Cancer. 2009;61(6):879-87. doi: 10.1080/01635580903285122.

Zinc in cancer prevention.

Prasad AS, Beck FW, Snell DC, Kucuk O.

Source

Wayne State University School of Medicine, Detroit, Michigan 48201, USA. prasada@karmanos.org

Abstract

Essentiality of zinc for humans was discovered 45 yr ago. Deficiency of zinc is prevalent world wide in developing countries and may affect nearly 2 billion subjects. The major manifestations of zinc deficiency include growth retardation, hypogonadism in males, cell-mediated immune dysfunctions, and cognitive impairment. Zinc not only improves cell mediated immune functions but also functions as an antioxidant and anti-inflammatory agent. Oxidative stress and chronic inflammation have been implicated in development of many cancers. In patients with head and neck cancer, we have shown that nearly 65% of these patients were zinc deficient based on their cellular zinc concentrations. Natural killer (NK) cell activity and IL-2 generation were also affected adversely. Th2 cytokines were not affected. In our patients, zinc status was a better indicator of tumor burden and stage of disease in comparison to the overall nutritional status. Zinc status also correlated with number of hospital admissions and incidences of infections. NF-kappa B is constitutively activated in many cancer cells, and this results in activation of antiapoptotic genes, VEGF, cyclin DI, EGFR, MMP-9 and inflammatory cytokines. Zinc inhibits NF-kappa B via induction of A-20. Thus, zinc supplementation should have beneficial effects on cancer by decreasing angiogenesis and induction of inflammatory cytokines while increasing apoptosis in cancer cells. Based on the above, we recommend further studies and propose that zinc should be utilized in the management and chemoprevention of cancer

Exp Gerontol. 2008 May;43(5):370-7. Epub 2007 Nov 1.

Clinical, immunological, anti-inflammatory and antioxidant roles of zinc.

Prasad AS.

Source

Wayne State University School of Medicine, Detroit, MI 48201, USA. prasada@karmanos.org

Abstract

The essentiality of zinc for humans was recognized only 40 years ago. Zinc deficiency was suspected to occur in Iranian patients with growth retardation, hypogonadism in males, hepato-splenomegaly, rough and dry skin, geophagia and severe iron deficiency anemia. Later

we documented zinc deficiency in similar patients in Egypt. The diet of these patients consisted of mainly cereal proteins which contained high phytate and this led to decreased availability of iron and zinc. These patients had severe immune dysfunctions, inasmuch as they died of intercurrent infections by the time they were 25 years of age. In our studies in experimental human model of zinc deficiency, we documented decreased serum testosterone level, oligospermia, severe immune dysfunctions mainly affecting T helper cells, decreased serum thymulin activity hyperammonemia, neuro-sensory disorders and decreased lean body mass. The basic mechanisms of zinc action on immune cells have been reviewed in this paper. Our studies showed that the activation of many zinc dependent enzymes and transcription factors were affected adversely due to zinc deficiency. The gene expression and production of Th1 cytokines were affected adversely due to zinc deficiency. Zinc is also an antioxidant and has anti-inflammatory actions. We have reported decreased plasma zinc, increased plasma oxidative stress markers and increased generation of inflammatory cytokines in the elderly subjects which were corrected by zinc supplementation. In cell culture studies, we have observed that zinc induces A20 which inhibits NF-kappaB activation resulting in decreased generation of inflammatory cytokines