Session 11. METAL IONS IN ONCOLOGY: CARCINOGENESIS AND ANTITUMOUR EFFECTS

CANCER PREVENTION BY SELENIUM

[1] G.F. Combs, Jr., [2] L.C. Clark, [3] B.W. Turnbull

[1] Division of Nutritional Sciences; [3] School of Operations Research, Cornell University, Ithaca, New York, USA; [2]deceased, formerly Arizona Cancer Center, University of Arizona, Tucson, AZ, USA.

Background: The nutritional functions of the trace element selenium (Se) are thought to be discharged by a fairly small number of selenocyteine-containing proteins. These include some that function in antioxidant protection (glutathione peroxidases) and redox regulation (thioredoxin reductases), and others involved in the thyroid hormone production (iodothyronine 5'-deiodinases). That Se supplements can reduce tumor yields in animal models and cancer risk in humans whose dietary intakes of Se are apparently adequate to support the full expression of these selenoproteins, suggests that Se affects carcinogenesis via mechanisms independent of those proteins, i.e., involving specific Se-metabolites. While it cannot be excluded that cancer protection may involve selenoenzymes, such effects might be expected to function in anti-initiation. However, the limited number of human trials completed to date indicate late-stage, cancer-protective effects of Se involving such mechanisms as enhanced immune surveillance, altered cell cycle regulation and enhanced apoptosis. We conducted The Nutritional Prevention of Cancer Trial to determine whether the regular use of supplemental Se (200 ug/day, as a Se-enriched yeast product) by free-living older Americans could reduce cancer risk.The results of the first 10 yrs of this Trial were reported in 1996.

Aims: This report presents the results of the complete Trial.

Methods: We performed analyses of all 13 yrs of the intervention phase of the Trial, and conducted analyses of baseline Se and vitamin E status as covariates of the effect of supplemental Se on prostate cancer incidence.

Results: We found that the use of supplemental Se by Americans with plasma Se levels averaging ca. 120 ug/ml (which suggested an average dietary intake of at least 85 ug Se/day) showed significant reductions in total carcinomas and cancers of the prostate and colon. In the case of prostate cancer, for which Se treatment was associated with a 67% reduction in cases diagnosed, apparent protection was observed within the first 2-3 yrs of the trial. Protection by Se appeared limited to subjects who entered the trial with plasma Se concentrations below ca. 120 ng/ml and with plasma vitamin E levels below the median, 11 ng/ml for the population.

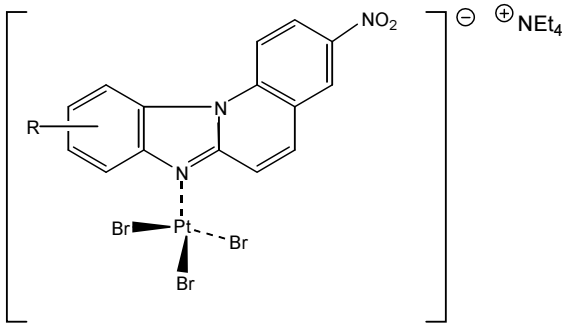
Conclusion*:* Because most healthy people worldwide have plasma Se levels less than that level, it is likely that increasing Se intakes, either through supplementation, food fortification or the production of Se-enriched crops, may be effective in reducing cancer rates in most countries.

NEW CYTOTOXIC TRIBROMOPLATINATE (II) COMPLEXES CONTAINING BENZIMIDAZO[1,2-*A*]QUINOLINES LIGANDS: SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL STUDIES

[1] E.Y. Correa, [1] O.Cox, [2] M. Cordero, [2] F.A. Gonzбlez

[1] MIE Program, Department of Science and Technology, Universidad Metropolitana, PO Box 21150, San Juan, Puerto Rico, [2] Department of Chemistry, University of Puerto Rico, PO Box 23346, San Juan, PR 00931-3346 USA.

Work in our laboratory has shown that benzimidazolo[3,2-*a*]quinolinium salts (**1**) are potentially useful antineoplastic agents. It is also well established that platinum(II) complexes are active against tumor cells lines. Therefore we decided to prepare tribromoplatinate (II) complexes incorporating benzimidazo[1,2-*a*]quinoline (**2**) as ligands of the type $[NEt_4][Pt(L)Br_3]$ in order to assess the a possible synergistic effect between **1** and the and platinum(II) complexes. The complexes were prepared by the symmetric cleavage of the binuclear bromo-bridged complex $[NEt_4]_2[Pt_2Br_6]$ its reaction with either 3-nitro- or 3-nitro-8,9-dimethylbenzimidazo[1,2-*a*]quinolines (**2a** and **2b**, respectively) in acetone



2a: R =H
2b: R = 9,10-diCH_3

solution at 50°C to yield **3a** and **3b**, respectively. The cytotoxicity of **3a** and **3b** was compared to that of the parent quinolines (**2a**) and with its protonated form 7(H)-3-nitrobenzimidazolo[3,2-*a*]quinolinium chloride (**2c**). The IC_{50} (μM) of **2a, 2c, 3a** and **3b** against U937 cell line are: >950, >780, 2.8 and 4.5, respectively. Two important results emerge from this research: **3a** and **3b** are more active than 7-(1-propenyl)-3-nitrobenzimidazolo[3,2-*a*]quinolinium chloride (IC_{50} (μM) = 23.7±7), the most active derivative of **1** previously reported by us, and more importantly, they are active against a cell line resistant to cisplatin. All new compounds were characterized by elemental analyses and spectroscopic methods (FT-IR, UV-*vis* and 2D NMR).

METAL IONS AND CANCER

[1] B. Desoize, [2] Ph. Collery

[1] Laboratoire Biochimie, EA 3306, Faculty de Pharmacie, IFR 53, 51 rue Cognacq-Jay 51000 Reims, France; [2] Service de Cancйrologie, Polyclinique Maymard, rue Marcel Paul, 20200 Bastia, France.

Several metals and metal containing compounds are potents mutagens and carcinogens. The most often blamed are chromium, arsenic, nickel, vanadium, iron, copper and manganese. Although each of them has its own mechanism of action, it is believed that most of their mechanisms of action involve reactive oxygen species (ROS). In certain type of cells, ROS amplifies or potentiates the transcription factor NFκB activation. Furthermore, nickel modulate gene expression by induction of DNA methylation and/or suppression of histone acetylation. Arsenic activity on cell metabolism is multiple, it seems that cell transformation is induced by long-term exposure to low level of arsenic. The paradox of arsenic is that it has also a valuable therapeutic efficacy in cancer treatment. The actions of arsenic are related to cell type, chemical species and length and dose exposure. Manganese is known to cause DNA damage and chromosome aberrations, although, it should be noticed that it would not represent a significant carcinogenic risk to the population and workers.Metal compounds are used in medicine since decades, or even centuries: gold (anti-artritic), iron (anti-malarial), bismuth (anti-ulcer), silver (antimicrobial), antimony (anti-protozoal) and platinum as anti-cancer. Magnesium seems to protect cells from cancer and conversely, iron seems to facilitate cell proliferation, then, magnesium deficiency and iron excess are not exactly carcinogenetic, but certain concentrations of these metal ions are needed to avoid cancer.The only metal officially used in cancer treatment is platinum. Although a large amount of research has been performed, only four platinum derivatives are allowed, today, to be used in the clinic. The second metal used in human is gallium. The results are promising, the mechanism of action is, at least partly, explained by its competitivity for iron. Pure chelators of iron show also anticancer effects. A great number of gold derivatives have shown clear activity against tumour cells, including cisplatin-resistant cancer cells. Bismuth and antimony yield interesting activity *in vitro*, but they are relatively unexplored. Ruthenium, titanium and rhodium compounds have shown also anticancer activities, there mechanisms of action appeared to be mostly analogue to those of platinum; they could be in fact prodrugs, there hydrolysis products could be the active drugs. The activities of vanadium are multiples: it inhibits synthesis of carcinogens-derived active metabolites, it inhibits tyrosine phosphatases and activates tyrosine phosphorylases, it modulates expression of cellular adhesive molecules and reverses notably antineoplastic drug resistance, with an overall low toxicity. Since its infancy, humans are in contact with metal. As shown above, some metals are dangerous, other can cure diseases. Will the absolute treatment against cancer be found amongst metal ions or derivatives? The response could be positive, but much work must still be done.

SELENIUM AND PROSTATE

[1] R.M. Pйrez-Beriain, [1] A. Garcна de Jalyn Comet, [1] J. Castrillo, [1] M.L. Calvo Ruata, [2] J.F. Escanero, [3] A. Garcна de Jalyn Martнnez, [3] A. Borque, [3] C. Allepuz

[1] Biochemistry department, Miguel Servet Hospital, [2] Physiology Department of University Zaragoza, Spain, [3] Urology Department Miguel Servet Hospital, Zaragoza, Spain.

Background**:** Prostate cancer is the second leading cause of cancer deaths in men, therefore it is increasingly important to understand its biology and epidemiology. Subjets with high selenium and vitamin E intake have a lower risk of prostate cancer. The risk of cancer for patients with low serum selenium has been estimated to be up to twice that of subjets with higher levels. Selenium supplementation has recently been shown to decrease total cancer incidence. However, the mechanism of action of selenium as an anticarcinogenic agent has yet to be elucidated.

Aims: The aim of the study was to investigate the possible relationship between selenium levels in prostate cancer patients and the healthy population.

Materials and Methods: We considered 197 patients with benign prostatic hyperplasia, and 66.25 ± 5.11 years old. By other side, we included 116 patients with positive prostatic biopsy (prostate cancer) and

69.19 ± 8.08 years old.

The serum selenium levels were measured by atomic absorption spectrophotometry (AAS) with a graphite furnace and Zeeman background corrector (*Perkin Elmer 4110 ZL*), using $Pd(NO_3)_2$ solution as matrix modifier.

The statistical calculations were carried out using SPSS statistics program. The statistical test used has been the Student T-test for equality of means.

Results: According to age, the differences are not statistically significant. Selenium concentrations in the benign prostatic hyperplasia group, 75.54 μg/l. And, in prostate cancer group were 69.90 μg/l. The means comparison shows a statistically significant difference with a $p<0.05$.

Conclusions: The findings of this study suggest that the individuals with prostate cancer show lower serum concentrations of selenium than benign hyperplasia.

TWO NEW VANADYL(IV) COMPLEXES WITH POTENTIAL ANTINEOPLASTIC EFFECT ON OSTEOBLASTS IN CULTURE

[1,2] S. B. Etcheverry, [1] D.A. Barrio, [1] M.S. Molinuevo, [1] A.M. Cortizo

[1] Bioquнmica Patolygica; [2] CEQUINOR, Facultad de Ciencias Exactas, Universidad Nacional de La Plata. 47 y 115 (1900) La Plata, Argentina. E mail: etchever@biol.unlp.edu.ar

Vanadium compounds have been shown to possess pronounced antineoplastic activity both in vivo and in vitro. As part of a project devoted to the development of new vanadium derivatives with potential therapeutical applications, two vanadyl(IV) complexes, one with glucose (GluVO) and the other with naproxen, an anti-inflammatory drug (NapVO) were synthesized and thoroughly tested on osteoblasts in culture. Rat osteosarcoma (UMR106) and mouse calvaria (MC3T3E1)-derived cells were incubated with different concentrations of GluVO and NapVO. Both compounds inhibited cell proliferation (crystal violet bioassay) with higher potency on UMR106 tumoral cells than on the non-transformed osteoblasts. GluVO behaved as a more potent inhibitory agent than NapVO. The differentiation of MC3T3E1 cells (alkaline phosphatase activity) was not significantly affected by these vanadium derivatives. On the contrary, both vanadium compounds inhibited UMR106 differentiation with similar potency, in a dose response manner. In addition, both compounds caused morphological alterations and lipid peroxidation (thiobarbituric reactive substances, TBARS). The levels of TBARS increased in a manner dependent on the concentration of vanadium. Both vanadyl(IV) complexes strongly enhanced the phosphorylation of external regulated kinases (P-Erks). In conclusion, NapVO and GluVO caused osteoblast cytotoxicity and morphological alterations with stronger effects on tumoral than on non-transformed osteoblast-like cells, being potentially useful compounds for antitumoral therapy.

EFFECT OF GALLIUM ON THE GROWTH RATE OF U937 CELL CULTURE AND THE ACTIVITY OF TYROSINE KINASE

[1] B. Farzami, A. Pournaki, [2] P. Collery, [3] G. Bahram

[1] Department of Clinical Biochemistry, Tehran University of Medical Sciences P.O.Box 14155-5399 Tehran Iran; [2] Service de Cancerologie, Polyclinique Maynard 20200 Bastia France; [3] Institute of Biophysics and Biochemistry Tehran University, Iran.

In our study U937 cell, a human myeloid leukemic cell line, has been used to show the effect of Gallium on cellular growth and Tyrosine kinase activity. These cells were cultured in a medium composed of RPMI 1640 (50%) FCS (10%) and deionized water (40%). The study was performed in two steps, and in every step two cultures containing $5x10^5$ / m.l cells as controls and samples containing 200 and 400 μM Gallium Chloride was used. The cultures were counted and assessed for viability at hours 24, 48, 72, 144, 168. IC50 of 72 hrs and 24 hrs. were obtained for the concentrations of 200 and 400 μM, respectively. Tyrosine kinase assay was performed by ELISA on the cell free system of the two specimen showed a concentration dependent increase in the level of tyrosine kinase in Gallium teated cells.

EXPOSURE TO DIFFERENT NICKEL COMPOUNDS AND RISK OF LUNG CANCER

[1] T.K. Grimsrud, [2] S.R. Berge, [1] T. Haldorsen, [1] A. Andersen

[1] Kreftregisteret (The Cancer Registry of Norway), Institute of Population-Based Cancer Research; Montebello; N-0310 Oslo; Norway; [2] Falconbridge Nikkelverk A/S; Environment, Health & Safety Department; P.O. Box 604; N-4606 Kristiansand; Norway.

Background: Nickel compounds are classified as carcinogenic to humans, but it is not known with certainty which nickel compounds constitute the cancer risk.

Aims: A nested case-control study was performed in

order to examine the relationship between lung cancer risk and cumulative exposure to four groups of nickel compounds: water-soluble, sulfidic, oxidic, and metallic nickel.

Methods: A time- and department-specific exposure matrix was developed based on 5,900 personal measurements of total nickel and speciation analyses of refinery dusts and aerosols. The study comprised 213 out of 227 incident cases of lung cancer diagnosed between 1952 and 1994 and 525 age-matched controls (94% participation rate). Data on smoking habits were collected by interview with the person in question or his closest relative. Cumulative exposures were computed on the basis of exposure concentration and duration of work in each department.

Results: The nickel exposures were moderately to highly correlated. There were 98% and 82% smokers among cases and controls, respectively. A dose-related effect on lung cancer risk was seen from exposure to water-soluble nickel. No dose-dependent effect was seen from other forms of nickel, but a general increase in risk irrespective of dose could not be excluded. Smoking was a weak to moderate confounder. The risk from joint exposure to nickel and tobacco could be described in a multiplicative model.

Conclusion: The rise in lung cancer risk by increasing cumulative exposure to water-soluble nickel supported earlier findings among British, Finnish, and Norwegian nickel-refinery workers. The results suggest that the role of water-soluble species in nickel carcinogenesis may be more important than previously recognized.

THE EFFECT OF IRON ON PROSTATE AND BREAST CANCER CELL INVASION

A.A. Kajdacsy-Balla, S. Kaul, C. Chitambar, P.F. Lindholm

Departments of Pathology and Internal Medicine, Medical College of Wisconsin Milwaukee WI 53226, USA.

Whereas it has been known for sometime that malignant and nonmalignant cells require iron for their viability and proliferation, it has never been previously reported that iron may be a factor in tumor invasiveness and metastasis. In order to test this hypothesis, PC-3, a prostate cancer cell line, and MDA-MB-231, a breast cancer cell line were pre-exposed to various concentrations of iron salts, either ferric chloride or ferric ammonium citrate (FAC), and tested by assays for cell motility, invasion and adhesion. When compared to untreated cells in Matrigel® invasion assays, PC-3 cells treated with 100 μM FAC or 200 μM $FeCl_3$ had a 52 ± 18% and 122 ± 24% increase in invasion respectively ($n=8$, $p< 0.05$). Similar results were obtained for invasion of MDA-MB-231 cells treated with 200 μM FAC and above (205 ± 32%, $n = 5$, $p< 0.05$), but not with various concentrations of $FeCl_3$. Modified Boyden chamber cell motility assays showed 40 ± 5% increase in migration after cells were treated with 100 μM FAC for PC-3 cells ($n = 4$) and 105 ± 7% for MDA-MB-231 cells ($n = 4$). A 23 ± 6% increase in motility occurred with 200μM $FeCl_3$ for MDA-MB-231 cells ($n = 4$). Cell adhesion to Matrigel® substrate was not changed by FAC or $FeCl_3$ when adhesion was measured at either 15, 30 or 45 min. Concentrations of iron salts that were used in our studies are physiologically relevant, and at least 100-fold less than concentrations that caused loss of viability for these two cell lines. These results suggest that excess iron may have an enhancing effect on invasion and metastasis. This finding may have clinical relevance since epidemiological studies show an association between increased iron levels and iron saturation and increased risk of cancer occurrence and mortality. Postulated mechanisms by which increased dietary iron may enhance the risk of cancer development include the generation of DNA damaging oxygen free radicals and the promotion of cancer cell growth. In addition, we show that iron could possibly cause acceleration of cancer progression by enhancement of cell motility and invasion. We are now studying possible mechanisms for this effect of iron.

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BONE MINERAL DENSITY AND THE SUBSEQUENT RISK OF UTERINE CANCER IN THE NHANES I FOLLOW-UP COHORT

R.L. Nelson, M. Turyk, J. Kim, V. Persky

Department of Surgery & Department of Epidemiology and Biostatistics, University of Illinois, Hospital, 1740 West Taylor Street, Chicago, Illinois 60612, USA. E-mail: Altohorn@uic.edu VWPersky@uic.edu Mturyk1@uic.edu Jkim@siumed.edu

Bone Mineral Density (BMD), measured in 1975, significantly predicted the subsequent incidence of uterine cancer in the NHANES Epidemiologic Follow Up Cohort. This finding further supports BMD as a measure of estrogen exposure and also, inlight of negative data related to breast cancer, weakens the association of estrogen with breast cancer etiology.

RUTHENIUM SEMICARBAZONE COMPLEXES AS POTENTIAL ANTITUMORAL AGENTS

[1] L. Otero, [1] P. Noblia, [1] D. Gambino, [2] H. Cerecetto, [2] M. Gonzбlez, [3] A. Monge-Vega, [3] A. Lypez de Cerбin, [3] O. Ezpeleta, [4] B. Parajyn-Costa

[1] Cбtedra de Quнmica Inorgбnica, [2] Departamento de Quнmica Orgбnica, Facultad de Quнmica, Universidad de la Repъblica, CC 1157, 11800 Montevideo, Uruguay; [3] CIFA, Universidad de Navarra, Pamplona, Espaca; [4] CEQUINOR, UNLP, La Plata, Argentina.

These last decades have seen a growing interest in coordination compounds of transition metals as potential antineoplastic agents. Some promising results have been obtained with derivatives of different metals. In particular, several Ru complexes have exhibited good to excellent antitumoral activity in some tumor screens. On the other hand, 5-nitro-2-furaldehyde semicarbazone (Nitrofurazone®) has shown increased mammalian cell killing in hypoxia compared to aerobic conditions.[1] In this work, we have developed new Ru(II) complexes with Nitrofurazone® and its derivatives as an effort to combine free ligand and metal potential antitumoral activity. Complexes of general formulae $[Ru^{II}Cl_2(dmso)_2L]$, where dmso = dimethylsulfoxide and L = 5-nitro-2-furaldehyde semicarbazone and N^4-n-butyl-5-nitro-2-furaldehyde semicarbazone, were prepared in good yields by reaction of $[Ru^{II}Cl_2(dmso)_4]$ with L in ethanol or toluene solutions. FTIR and ^{1}H- and ^{13}C-NMR results were analyzed in detail. Chemical and structural results have been complemented with an evaluation of some physicochemical parameters (liposolubility, redox potential) and biological activity of the new complexes. The electrochemical behaviour was studied using cyclic voltammetry at different scan rates. Signals associated with the metal center and the ligand were observed. Compounds were tested in aerobic conditions against MCF-7 (human mammary adenocarcinoma) and TK10 (human kidney adenocarcinoma) tumor lines. Results showed no antitumoral activity in these conditions. The lack of activity could be related with the high hidrophilicity of the complexes. Selective citotoxicity studies in hypoxic conditions against V79 (chinese hamster fibroblastes) are still in progress.

ASSESSMENT OF SOME HEAVY METALS IN THE MATERNAL BODY, RISK IN CANCER DISEASE

C. Hura, I. Palamaru, B.A. Hura

Food Toxicology Laboratory, Institute of Public Health, Iassy, Romania.

Ever since humans have become aware that health is inseparably linked to an intact and healthy environment, the control and reduction of pollution have become the focus of world-wide concern. The studies on heavy metals concentrations in human placenta and human milk have been performed, as a continuation of the research conserning heavy metals concentrations in biological and in food samples by atomic absorption spectrophotometry method.The aim of thise study was the evaluation of the metals contents in the maternal body.

Material and Methods: The study presents the results obtained in 2000–2001 period of some metals [Pb, Cd, Zn, Cu, Mn] in maternal body, in Iassy district, it was investigated if heavy metals levels from human placenta and human milk reflect the body burden of these chemicals.A total of 50 women (18–30 years old) participated in the study voluntarily. The women were giving birth to their first or second child at "Cuza Voda" Hospital of Iassy in 2000–2001 (April –May) period.The milk samples had been collected manually preferentially before the infant was nursed in the morning.Trace elements concentrations were analysed by atomic absorption spectrophotometry, using a Carl Zeiss Jena, Model AAS-1N, with flame air-acethylene.

Results: In all analysed samples these metals were found. Generally, a wide variation between individual samples was observed.

Placenta: The mean metals levels in the maternal placenta varied between 0.2 μg/kg Cd and 8.18 μg/kg Zn.

Human milk: The results of the investigations showed a variation of heavy metals between 0.3 μg/kg Cd and 12.46 μg/kg Zn.

Conclusion: Determinations of these pollutants in human body are important in environmental monitoring for the prevention, control and reduction of pollution as well as for occupational health and epidemiological studies.

CISPLATIN-MEDIATED BIOCHEMICAL CHANGES IN MITOCHONDRIA IN TUMOR-BEARING MICE

S.B. Prasad, A. Kharbangar

Cell and Tumor Biology Lab., Department of Zoology, North-Eastern Hill University, Shillong-793022, India. E-mail: sbpnehu@hotmail.com

Cisplatin is an effective anticancer drug for the treatment of various malignancies. The ability of cisplatin to form cisplatin-DNA adducts is thought to be the main mechanism underlying its cytotoxic effect. It has also been observed that besides DNA, cisplatin affects host's immune response, cell surface, various enzymes, tissue calcium concentrations and mitochondria also which have let to the proposal of the involvement of multi-step and multilevel effects of cisplatin in the tumor cell/host during cisplatin-mediated chemotherapy against cancers. In view of the recent reports on the significance of mitochondria in tumorigenesis, maintenance of malignant phenotype and apoptosis, changes in mitochondrial(mt) glutathione, malate dehydrogenase and lipid peroxidation in a tumor-bearing mice were determined after cisplatin treatment. Swiss albino mice-bearing ascites Dalton's lymphoma (DL) were administered with cisplatin (8 mg/Kg body wt.). After 24, 48, 72 and 96h of cisplatin treatment, tumor, liver and kidneys were collected and mitochondrial fractions were isolated for the assay of these biochemical parameters. Cisplatin treatment of tumor-bearing mice resulted in a significant decrease of mt-protein and mt-glutathione in these tissues while mt-lipid peroxidation, an indicative of oxidative damage, increased in the tissues. Ultrastructural features revealed that mitochondria were enlarged, rounded with disorganized cristae following cisplatin treatment. The units of enzyme activity of malate dehydrogenase (MDH), an important constituent of malate-aspartate shuttle in mitochondria, was noted decrease after cisplatin treatment. The slight increase in the specific activity of MDH was seen after the treatment which could be due to a larger decrease of other proteins rather than MDH. It is thus, suggested that cisplatin-induced biochemical changes involving decrease of mitochondrial glutathione, protein and the concomitant increase in mt-lipid peroxidation along with changes/ decrease in MDH activity could be a critical event during cisplatin induced-toxicity/cytotoxicity in the host.

MUTAGENICITY AND ENDOGENOUS GLUTATHIONE LEVELS IN TUMOR-BEARING MICE AFTER CISPLATIN TREATMENT

S.B. Prasad, D. Khynriam

Cell and Tumor Biology Lab, Department of Zoology, North-Eastern Hill University, Shillong-793022, India. E-mail: sbpnehu@hotmail.com

Cisplatin is a potent anticancer drug but its therapeutic efficacy is limited due to the development of adverse side effects including mutagenicity. Glutathione (GSH), an important cellular antioxidant, has been reported to be implicated in the metabolism of cisplatin and tumor cell proliferation. Therefore, it could be of interest to determine cisplatin-mediated mutagenic/cytotoxic effects in relation to GSH changes in the host. Swiss albino mice-bearing ascites Dalton's lymphoma (DL) were administered with cisplatin (8 mg or 4 mg/Kg body wt.) or L-buthionine(S,R)-sulfoximine (BSO, 5 mM/Kg body wt, i.p., 8 h prior to cisplatin) plus cisplatin or cysteine plus cisplatin. After 24 to 96 h, 30 h and 10 days of cisplatin treatment chromosomal aberrations, micronuclei and sperm head abnormalities respectively were analyzed as the mutagenic parameters. Cisplatin treatment caused the development of chromosomal aberrations, micronuclei and sperm head abnormalities in a dose dependent manner. Total chromosomal aberrations/aberrant metaphases were much more in DL cells than that in bone marrow cells. These aberrations/aberrant metaphases were highest at 24 h of cisplatin treatment which decreased sharply in bone marrow cells, showing about 75% recovery but remained almost unchanged in DL cells during later periods of treatment. Abnormal sperms contained mainly amorphous and hooked heads. As compared to cisplatin alone, in the combination treatment with BSO plus cisplatin, an increase in the frequency of all the three mutagenic parameters was observed. However, in cysteine plus cisplatin-treated condition these mutagenic parameters were significantly decreased as compared to the respective treatment with cisplatin alone or BSO plus cisplatin. After cisplatin treatment of mice, a decrease in GSH levels was noted in bone marrow and DL cells which was further decreased in BSO plus cisplatin treatment condition. These findings suggest that the changes in glutathione levels may play an important role in the development of cisplatin-mediated mutagenic /cytotoxic effects in the host.

COMPLEXATION OF *N*-CARBOXYALKYL DERIVATIVES OF 3-HYDROXY-4-PYRIDINONES WITH Fe(III), Al(III), Ga(III) AND In(III) STUDIES IN *VITRO* AND IN *VIVO*

[1] M. A. Santos, [1] M. Gil, [2] M. Lurdes Gano, [1] S. Chaves

[1] Centro de Quнmica Estrutural, Complexo I, Instituto Superior Tйcnico, Av. Rovisco Pais, 1049-001 Lisbon, Portugal; [2] Instituto Tecnolygico e Nuclear Estrada Nacional Nє 10, 2686-953 Sacavйm, Portugal.

The development of chelating agents for Fe(III) and the group 13 (IIIA) metal ions is of biomedical interest, considering the number of inherited diseases that result of iron-overloaded in humans, the association of alu-

minium with neurological dysfunctions (renal dialysis encephalopathy) and the importance of radionuclides (^{67,68}Ga and ^{111}In) in diagnostic nuclear medicine. The 3-hydroxy-4-pyridinones (3,4-HP) are very effective chelators in the neutral range of pH and one of those compounds (Deferiprone) has even been proposed as a clinical chelating. As part of an ongoing project for the design and study of ligands for this set of highly charged metal ions, with potential clinical use, we have decided to study and describe herein the effect of changing the length of the alkylic chain of the *N*-carboxyalkyl substituents of 3,4-HP, on both the *in vivo* and the *in vitro* properties. Thus, a set of those ligands, 1-carboxyalkyl-2-methyl-3,4-HP (alkyl = ethyl, propyl and butyl) was prepared and their lipohydrophilic character as well as their interaction with Fe(III), Ga(III), Al(III) and In(III) was studied, in aqueous solutions. They all present higher affinity for these metal ions than Deferiprone, the formation constants of the complexes following the order β (FeL_3) > β (GaL_3) > β (AlL_3) > β (InL_3). The lipophilic character of the ligands and the stability of the complexes decrease with the increasing size of the alkylic chain. Results from the *in vivo* studies clearly evidence that the administration of any of the three chelators interfere in the normal biological distribution profile of the tracer enhancing the excretion of ^{67}Ga, leading to lower bone uptake and higher blood clearance with increasing size of the chain.

TRACE METALS IN NEUROBLATOMA CELLS AND TUMORS

[1] C. Sergeant, [2] B. Gouget, [1] M. H. Vesvres, [1] G. Deves, [1] M. Simonoff, [3] J. Benard

[1] Laboratoire de Chimie Nuclйaire Analytique et Bioenvironnementale, CNRS UMR 5084, Le Haut Vigneau, BP 120, 33175 Gradignan cedex, France; [2] Laboratoire Pierre Sьe, CEA/CNRS UMR9956, CE de Saclay 91191 Gif sur Yvette, France; [3] Laboratoire de Pharmacologie Clinique et Molйculaire, Institut Gustave Roussy, 39 rue Camille Desmoulins, 94800 Villejuif, France.

Neuroblastoma (NB) is a severe cancer form in early childhood. N-*myc* amplification, which results in overexpression of the N-myc protein, is causally involved in the progression of NB to advanced stages of malignancy. Iron is an essential element required for cell division and increased intracellular iron concentrations may promote malignant cell growth. N-*myc* amplified cells can synthesize zinc metalloenzymes allowing tumor invasion and metastases formation.

In previous studies, by using Proton-Induced X-Ray Emission (PIXE) technique with the nuclear microprobe, we showed that a relation exists between intracellular trace metal concentrations of cultured neuroblasts and the degree of N-*myc* oncogene amplification (Gouget B. et al., NIM B, 170 (1-4), 432-442, 2000). We started the measurement of trace metals in tumors formed by injection of these human neuroblastoma cells in athymic mice (Gouget B. et al., NIM B, 181, 465-469, 2001).

In order to confirm this relation, Fe, Cu and Zn concentrations have been measured in three other human neuroblastoma cell lines with different degrees of N-*myc* amplification and in the corresponding tumors. An original point is that one cell line is a non-amplified one transfected with N-*myc* gene.

These results should add important informations to understand the role of trace metals in human cancer cells.

SOLUBLE CELL ADHESION MOLECULE-1, SELENIUM AND DIET IN RENAL AND URINARY BLADDER CANCERS

[1] A.M. Witkowska, [2] B. Darewicz, [3] R. Markiewicz, [3] M.H. Borawska, [3] K. Hukaiowicz

[1] Department of Food Commodities Science and Technology, Medical Academy, ul. Mieszka I 4 b, 15-054 Biaiystok, Poland; [2] Urology Clinic, Medical Academy, ul. Skiodowskiej 24 a, 15-276 Biaiystok, Poland; [3] Department of Bromatology, Medical Academy, ul. Kilicskiego 1, 15-230 Biaiystok, Poland.

Soluble cell adhesion molecule-1 (sICAM-1) may play an important role in the cancer progression. Its elevated serum levels were observed in renal and bladder cancers. There is evidence that selenium is an antitumor factor. Though, in most papers low serum selenium has been reported. The purpose of the study was to analyze the influence of dietary preferences on serum sICAM-1 and selenium in renal and urinary bladder cancers. The serum sICAM-1 and selenium levels in 43 patients of both sexes (mean age 64) with urinary bladder or renal cell carcinoma, and in 15 controls (mean age 63) were measured. Serum selenium concentration was determined using electrothermal atomic absorption spectrometry. Serum sICAM-1 was determined with enzyme-linked immunosorbent assay (ELISA). Food-frequency questionnaires were implemented to collect the dietary data. The mean selenium concentrations in carcinoma of kidney and urinary bladder were higher than in controls ($p<0.005$ and $p=0.000001$, respectively). No difference was found between the two groups and controls with regard to sICAM-1. However, when men were excluded from the study, significantly elevated levels of sICAM-1 in women were observed at $p<0.002$. There was negative, but not significant, correlation between serum selenium and sICAM-1 levels in cancer patients ($r=-0.26$, $p<0.2$) and controls ($r=-0.34$, $p<0.4$). Significantly lower sICAM-1 level was observed in studied cancers, when alcohol was consumed more frequently. Frequent consumption of wholemeal bread was associated with statistically elevated serum selenium in subjects with renal and urinary bladder carcinoma. Our results suggest possible association between selenium, sICAM-1 and the diet in renal and urinary bladder cancers.