WA Cancer Research Symposium

Thursday 3 December 2009
Esplanade Hotel, Fremantle

Highlights

Morning Plenary Session
Professor Sanchia Aranda
Professor Barry Iacopetta

Morning, Afternoon and Lightning concurrent sessions showcasing current cancer research in WA

Afternoon Plenary Session
Professor Vincent Cogliano

Panel Discussion
Research 2010 and beyond
49. The effects of hormone depletion and phenoxodiol on prostate cancer cells and the Wnt signalling pathway

Larissa Wintle, Michael Millward, Arum M Dharmarajan, School of Anatomy and Human Biology, The University of Western Australia

Introduction: Androgen depletion therapy is the conventional treatment for advanced prostate cancer. However, the majority of tumours eventually continue to grow regardless of a low androgen environment. Alterations in pathways involved in the regulation of proliferation, apoptosis and survival, such as the Wnt signalling pathway, could be a mechanism by which prostate cancer can survive during androgen withdrawal. Chemotherapy is also a treatment option against prostate cancer; however, the existing treatments are limited in their effectiveness. Phenoxodiol (PXD) is a chemotherapeutic drug which has been shown to be an effective treatment in many cancer cell lines and is currently in early clinical trials for prostate cancer. This study aimed to determine the effects of hormone depletion and the effect of combining PXD and hormone depletion on LNCaP cells and on the Wnt signalling pathway.

Methods: The prostate cancer cell line LNCaP, were depleted of hormones via growth in charcoal stripped FBS-supplemented media. The LNCaP cells were also subjected to PXD treatment in combination with charcoal stripped media. After 48 hours of treatment, proliferation, apoptosis and changes in Wnt signalling were measured using Western blot analysis and qPCR.

Outcomes: Surprisingly, hormone depletion resulted in an increase in LNCaP cell proliferation and also an increase in apoptosis. This was associated with changes in Wnt signalling. Combining hormone depletion and PXD resulted in a reduction in proliferation.

Conclusions and Recommendations: The data suggested that androgen depletion could alter the Wnt signalling pathway. The data also suggest that PXD in combination with hormone depletion may be an effective treatment against prostate cancer.

50. Dietary intake of isoflavones and breast cancer risk by estrogen and progesterone receptor status

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Introduction: Epidemiological and experimental studies suggest that isoflavones may protect against breast cancer by acting as estrogen agonists or antagonists.

Methods: A case-control study was conducted in southeast China in 2004-2005 to examine the association between dietary isoflavone intake and breast cancer risk by estrogen receptor (ER) and progesterone receptor (PR) status. The incidence cases were 756 female patients with histologically confirmed breast cancer. The 1,009 age-matched controls were healthy women randomly recruited from outpatient breast clinics. We assessed isoflavone intake by face-to-face interview using a validated and reliable food-frequency questionnaire and obtained tumor ER and PR status from pathologic reports.

Outcomes: Compared to women in the lowest intake quartile, those in the highest quartile of total isoflavone intake had a reduced risk of all receptor status subtypes of breast cancer with a dose-response relationship. The adjusted ORs (95% CIs) were 0.39 (0.27-0.58) for ER+, 0.32 (0.21-0.49) for ER-, 0.43 (0.29-0.64) for PR+, and 0.30 (0.19-0.45) for PR- (p for trend <0.001). These inverse associations existed in both pre- and post-menopausal women after stratification. Stronger evidence of a protective effect of high isoflavone intake was observed for breast cancer tumours with concordant rather than discordant receptor status; i.e., those with ER+/PR+ (OR 0.39, 0.26-0.59) and ER-/PR- (OR 0.28, 0.17-0.44).

Conclusion & Recommendations: The finding that isoflavones protect against all tumor subtypes of breast cancer have biological plausibility, being supported by evidence from experimental studies. Future studies are required to fully understand the complex regulation of isoflavone on breast cancer by tumor hormone status.

51 Diesel exhaust, nitro-PAHs and cancer risks

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Introduction: Diesel vehicles are not only the dominant vehicle type used in heavy transport activities but also being widely used in light transport activities. Diesel exhaust consists of toxicants and carcinogens from both gaseous and solid phases such as NOX, COx, Polyacrylamid carboxylic hydrocarbons (PAHs) and nitro-PAHs. Nitro-PAHs are potent mutagens and probable carcinogens derived from PAHs but evidence from human studies is relatively rare. There are few available methodologies being applied to quantify internal exposure levels of individual nitro-PAHs from diesel exhaust. The aim of this pilot study is to develop appropriate methodologies to measure metabolites of nitro-PAHs as internal diesel exposure indicators.

Methods: PubMed, Ovid, ISI, Science Direct and other databases were used to obtain relevant research references. A gas chromatography mass spectrometry (GC-MS) approach was used to measure urinary 1-amino-9,10-phenanthrene (1-AP), a metabolite of 1-nitropyrene (1-NP) and 3-aminoanthracene (3-AAA), a metabolite of 3-nitroantracene (3-NA). The method was applied to measure the concentration of these analytes in urine samples collected from 18 subjects (including controls).

Outcomes: Nitro-PAHs in the atmosphere can be formed by radical-initiated reactions as secondary pollutants or by electrochemical nitration of PAHs emitted from diesel engines. The urinary detection limit for 1-AP was 50 ng/mL and that of 3-AAA was 250 ng/mL for a 10 mL sample size. The recovery rates of 1-AP were 66%-80% and that of 3-AAA were 64%-127%.

Conclusion & Recommendations: Developing innovative instruments and methodologies to quantify diesel exhaust exposure is an urgent initial step requiring further investigation. It is still too early to comment on current obtained results. The method will be further finalized and validated, and will be applied along with other indicators as an assessment tool to provide research evidence for the relationship of diesel exhaust and its potential cancer risks on humans.

52. Calixarene platforms for targeted delivery of anticancer agents

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Introduction: It has been proposed that the tumor site-selective delivery of anticancer drugs could be utilized to alleviate many of the serious and unpleasant side effects associated with the indiscriminate targeting of rapidly dividing cells by common cytotoxic drugs, such as paclitaxel. Exploring differences between normal and cancer cells, such as the upregulation of membrane folate receptors in some cancers, may afford some selectivity towards the latter. Direct conjugation of anticancer drugs to folic acid, the endogenous ligand for the folate receptor, has widely been investigated with many promising results. However, the low drug payload per endocytic cycle limits cellular drug uptake and significantly decreases drug efficacy. An alternate approach has been to conjugate folic acid onto a nano-scale assembly, such as polymeric micelles or nanoshells, which can carry a higher drug payload. A potential carrier is the calixarenes, which are well known to retain guest molecules within its cavity, and are capable of forming stabilized larger spherical assemblies of ~30 nm. In this paper, we report on the preparation of calix[4]arenes modified with folic acid and sulfonate moieties to impart cancer targeting functionality and water solubility, respectively.

Methods: Both the upper and lower rims of the calix[4]arene were modified by established methods to allow for the conjugation of folate acid and sulfonate groups. Identity and purity of products were confirmed by NMR, IR and MS.

Outcomes: Water-soluble folate-functionalized calixarenes can be prepared as a cancer targeting drug delivery platform. It has potential applications for paclitaxel, whose lack of specificity and intracellular target benefit from selective folate-mediated uptake into cancer cells, and whose intractable aqueous solubility is resolved by loading into a water-soluble carrier.

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