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Aldosereductase (AR) activity in RBCs and AR activity and expression in human breast cancer

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Background: Cancer is one of the leading causes of human morbidity and mortality around the world and breast cancer, commonest in females. The Aldo-keto-reductase (AKR) family has about 140 proteins including Aldose reductase (AR or AKR1B1) and AR like proteins (AKR1B10). AR is the rate-limiting polyol pathway enzyme that converts glucose into sorbitol and is known to be involved in the secondary complications of diabetes.AR is also upregulated in many cancer cells and is thought to be involved in their resistance to chemotherapeutic drugs.

Objectives:To studythe Specific activity of AR in RBCs and the Specific activity and expression of AR and AKR1B10 in breast tumorand non-tumor areas.

Methodology:Whole blood samples were collected from 60 breast cancer patients and 60 non-cancer controls.A total of 100 fresh post-surgical tumor tissues, which also included 25 benign tumors were obtained. AR activity was studied in RBCs while both AR and AKR1B10 were studied by immunoblotting [for expression] and enzyme activity studies in tissue samples. Histopathology evaluation for typing and grading of tumors was also done. Statistical analysis was done usingMann-Whitney U- test.

Results: Specific activity of AR in RBCs of all cancer patients (of all grades)was significantly increased compared to benign and controls. Specific activity and expression of ARand AKR1B10 levels were increased in tumors compared to non- tumor samples.

Conclusions: Our study indicates for the first timethat increased AR activity levels in RBCs correlated with increased levels in tumorsand may be useful as an indicator to denote a possible development of breast cancer, which could alert the individual to seek medical opinion at an early stage and improve quality of life in such subjects.

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Using the gene expression signature of scutebarbalactone VN isolated from Scutellaria barbata to elucidate its anticancer activities

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Bioassay-guided fractionation led to the discovery of a novel neo-clerodane diterpenoid, scutebarbalactone VN (BalA: 8, 13-epoxy-3-en-7-hydroxy-6, 11-O-dibenzoyl-15, 16-clerodanolide), from the whole-plant methanol extract of Vietnamese Scutellaria barbata D. Don. A microarray technique combined with bio-informatic analyses showed that BalA could inhibit cell cycle pathways by down regulating genes such as CDC25A and AURKA. BalA also showed the potential to reactivate down regulated genes in hepatocellular carcinoma cells and genes in antioxidant pathways such as HMOX1 and HSPA1A. Querying Connectivity map 2.0 resulted in a match of the BalA-modulated gene signature with that of the 10 known compounds, most of which are currently marketed chemotherapy drugs. The highest matching scores belonged to lomustine, semustine, and withaferin A. Lomustine and semustine were found to alkylate DNA and RNA molecules, while withaferin A inhibits nuclear factor kappa B (NF-κB) activity. A luciferase reporter assay was also conducted on 293/NF-κB human embryonic kidney cells that had been transfected with the NF-κB-luciferase plasmid to verify the anticancer activity of BalA. The assay showed that Ba1A effectively blocked NF-κB with an IC50 of 38.60±0.05 μM.

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