Title
Pro-Oxidant Properties of Melanosomal Melanin from Melanoma Origin

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Authors
Meyskens, FL
Gidanian, S
Farmer, P

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differentiate pathways which may play a role in MnSOD upregulation, we studied both the NFκB and RAR-α pathways. Using a reporter construct, driven by an intronic fragment known to contain the NFκB consensus sequence within the MnSOD gene, we show a contribution from the NFκB element. In addition, studies using dominant-negative constructs to RAR-α suggest a decrease in ATRA-mediated increases in MnSOD protein levels. Upregulation of MnSOD is known to occur as a result of changes in cellular redox status. Our studies show a time-dependent increase in protein carbonyl and 4-HNE adducted proteins with a decrease in GSH and copper-zinc superoxide dismutase levels upon ATRA administration. Taken together, these studies show alterations in cellular redox status as a result of ATRA administration followed by upregulation of manganese superoxide dismutase which may contribute to chemoresistance in neuroblastoma (Supported by 1P20RR020180).

Role of Arginine Metabolizing Enzymes and NADPH Oxidase in Statin-Induced Tumor Cell Cytotoxicity

Srigoeridhar Kotanraju1, Jacek Zielonka1, Megan Bright1, Carol Williams1, and B. Kalayjianaranan1
1Medical College of Wisconsin

Statins (e.g., fluvastatin, simvastatin) inhibit the enzyme HMG-CoA reductase leading to decreased cholesterol synthesis. Statins also elicit vasoprotective, cardioprotective, and chemopreventive/chemotherapeutic effects that are independent of cholesterol-lowering effects (i.e., pleiotropic effects). This study is focused on understanding how statins exert cytotoxicity in breast adenocarcinoma cells (MCF-7 and MDA-MB-231). Both simvastatin and fluvastatin elevated nitric oxide (NO) in MCF-7 cells through stimulation of inducible nitric oxide synthase (iNOS). Statins along with sepiapterin (NOS co-factor) supplementation induced tumor cell death to a greater extent which was partially reversed by 1400W (specific inhibitor of PKA). These results suggest the involvement of protein isoprenylation in statin-induced cytotoxic effects in MCF-7 cells. However, statins (fluvastatin and simvastatin) downregulated iNOS and decreased NO production in MDA-MB-231, a metastatic breast cancer cell line. NO induces tumorigenesis in metastatic cancer cells. Both statins suppress the arginase activity in both cell types leading to decreased synthesis of polyamines and decreased cell proliferation. Statin-treatment inhibited superoxide formation via downregulation of the NADPH oxidase enzyme and decreased transferrin receptor expression in breast cancer cells. Isoprenylation inhibitors, especially the geranylgeranyltansferase inhibitor, mimicked statin-mediated effects. In conclusion, we report that statin’s ability to regulate arginine metabolizing enzymes and NADPH oxidase is critical to elucidating its mechanism of cytotoxicity in breast cancer cells.

Curcumin Induced G2/M Arrest and Apoptosis by Enhancing Superoxide Generation and Inhibiting Akt Activity in Chemoresistant Human Ovarian Cancer Cells

Vijay Kumar Kutala1, Selvendran Karuppayah1, Nathan M. Weir1, Liyue Tong2, Shilpa Viswanath3, and Periannan Kuppusamy1
1Center for Biomedical EPR Spectroscopy and Imaging, Ohio State University, Columbus, Ohio

Curcumin, a major active component of turmeric, is well known to induce apoptosis in several cancer cells, but little is known about its activity in chemo-resistant cells such as cisplatin-resistant ovarian cancer cells. Hence the aim of the present study was to investigate the anticancer properties of curcumin in cisplatin-resistant human ovarian cancer cells in vitro. The results indicated that curcumin inhibited the proliferation of both cisplatin-resistant (CR) and sensitive (CS) human ovarian cancer cells with almost equal sensitivity. Enhanced superoxide generation was also observed in both CR and CS cells treated with curcumin but not in normal ovarian cells. Curcumin induced G2/M phase cell-cycle arrest in CR cells by enhancing the p53 phosphorylation. Curcumin induced apoptosis by the activation of caspase-3 followed by PARP degradation. The phosphorylation of Akt and ERK1/2 was inhibited while the phosphorylation of p38 MAPK and p53 was enhanced. Pretreatment with N-acetylcyctiste attenuated the curcumin-induced inhibition of proliferation, caspase-3 activity and PARP degradation. In summary, our results showed that curcumin inhibited the proliferation of cisplatin resistant ovarian cancers through the induction of superoxide generation, G2/M arrest and apoptosis.

The Regulatory Subunit Vb of Cytochrome C Oxidase is Required for Malignant Transformation

Kristin Nelson1, Jian Li Campian1, and Jason Chesney1
1University of Louisville

Cytochrome c oxidase (COX) is an enzyme complex within the electron transport chain that is central to the regulation of aerobic metabolism. Recently, the expression of the nuclear encoded regulatory COX subunit Vb was found to be markedly increased in several tumor tissues as compared to matched normal tissues. The oncogene ras is activated in ~ 30% of all human neoplasms and is known to increase oxygen consumption in immortalized cells. We hypothesized that ras may increase oxygen consumption through upregulation of COX Vb expression. We found that ectopic expression of ras in immortalized human