and delphinidin (del) were found to inhibit tumor cell growth in-vitro in the low micromolar range. Both compounds represent highly potent inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR). The presence of vicinal hydroxy substituents at the phenylring in 2-position (B-ring) appears to play acrucial role for the interaction with the EGF-receptor. Malvidin, bearing two methoxy substituents at the B-ring, was found to be inactive up 100 μM. However, also malvidin exhibited substantial growth inhibitory properties. These results indicate that especially in the case of malvidin other cellular targets contribute tocell growth inhibition. The MAP kinase pathway represents one of the major signaling cascades regulating cell proliferation. Effective inhibition of the upstream located EGF-receptor results in a shut-off of the subsequent kinase cascade. In intact cells anthocyanins were found to influence the signaling cascades downstream of the EGFR. This was measured as phosphorylation of the transcription factor Elk-1. Cy and del inhibit Elk-1 phosphorylation in the concentration range where growth inhibition is observed. Thus, the anthocyanidins cy and del are potent inhibitors of the EGFR, triggering downstream signaling cascades. Interestingly, malvidin, lacking EGFR-inhibitory properties, also affects Elk-1 phosphorylation. The MAP kinase cascade is connected with several other signaling pathways in a complex network of crosstalks. One important regulative factor is the deactivating phosphorylation of the serine/threonine kinase Raf-1 byprotein kinase A (PKA), a key element of the cAMP-pathway. A central element in the cAMP homeostasis represents the superfamily of cAMP-hydrolysing phosphodiesterases (PDE). We showed previously that the cAMP-specific PDE isoenzyme family PDE4 represents the highest cAMP-hydrolysing activity in many human tumor cells. Selective inhibition of PDE4 in these tumor cells results in growth inhibition, arrest in the G_1-phase of the cell cycle and induction of apoptosis. Compared to the results obtained for the inhibition of EGFR activity, a completely different pattern of activity was observed investigating the effect of anthocyanins on PDE4 activity. Malvidin potently inhibits the cAMP hydrolysis of PDE4 isolated from solid human tumor tissue (IC_{50}= 32,7 ± 3,2 μM). In contrast, cy and del even enhanced PDE4 activity at low substance concentrations. The effective inhibition of PDE4 activity by malvidin might explain the effect of the compound on Elk-1 phosphorylation without EGFR-inhibitory properties. These results show that depending on the substitution pattern at the B-ring anthocyanidins affect different cellular targets crucial for the regulation of cell proliferation. The growth of human tumor cells is inhibited in the low mikromolar range, indicating that anthocyanins might be of interest in terms of chemoprevention.

A188 Berry Extracts Inhibit Activating Protein 1 (AP-1) Function and Cell Transformation by Perturbing the Mitogenic Signaling Pathway. Rentian Feng, Linda L. Bowman, Yongju Lu, Vince Castranova, Min Ding. *CDC-NIOSH, Morgantown, WV.*

Berry extracts, such as blackberry (BB) and strawberry (SB), are natural rich sources of bioflavonoids and phenolic compounds. These compounds are commonly known as potential cancer chemopreventive agents. Early studies indicated that berry-extracts exhibit antioxidant and antitumorogenic activities *in vitro* and *in vivo*. The molecular mechanisms of their actions remain unclear. In this study, we investigated the effects of berry extracts on cancer cell growth and cell transformation induced by 12-O-tetradecanoylphorbol-13-acetate (TPA). The underlying mechanisms of chemoprevention, including suppression of oxidative DNA damage and blockage of the transactivation of activator protein 1 (AP-1) as well as associated signal transduction pathways, were also explored. At the cellular level, the berry extracts inhibited the attachment and growth of lung-cancer cells. Results of the soft agar assay indicated that both BB and SB decreased TPA-induced neoplastic transformation of JB6 P+ cells in a dose-dependent manner. Pretreatment of A549 cells with BB or SB resulted in an inhibition of 8-hydroxy-2'-deoxyguanosine formation induced by UVB irradiation. Pretreatment of JB6 cells with berry extracts also resulted in an inhibition of UVB- or TPA-induced AP-1 transactivation. BB or SB treatment of JB6 cells inhibited the phosphorylation of extracellular signal-regulated kinases (ERKs) and c-Jun NH(2)-terminal kinases (JNKs), but not p38 kinase. Together, these results suggest that BB and SB exhibit potent chemopreventive activity. The possible mechanism by which BB and SB suppress JB6 cell transformation appears to involve the inhibition of AP-1 transactivation as well as its upstream MAPK family members, including ERKs and JNKs.

POSTER SESSION A

EXPERIMENTAL/MOLECULAR CHEMOPREVENTION: Proteomics, Chemogenesis, and Chemoinformatics

A189 Selenium and genomics: a pas de deux to cancer control. Yan Dong, Haitao Zhang, Clement Ip. *Roswell Park Cancer Inst., Buffalo, NY.*

Microarray technology is a powerful tool for genome-wide analysis of gene expression patterns. A major challenge is the ability to dissect meaningful information out of the large dataset generated from the microarray output. The current study presents a novel approach of using microarray data to characterize molecular targets of chemoprevention. In our effort to investigate the mechanism of selenium-induced growth arrest in prostate cancer cells, we profiled the gene expression changes in methylseleninic acid-treated PC-3 cells with the Affymetrix human genome U95A chip after 3, 6, 12, 24, 36 or 48 hr of exposure. The expression of a large number of genes with diverse biological functions was changed in response to selenium. Genes that were coordinately regulated were then clustered together by using the Self Organizing Map clustering algorithm. A possible explanation for co-regulation of genes in the same cluster could be due to the fact that these genes share common regulatory motifs in the promoter regions. To test this hypothesis, the accession numbers of a cluster of early selenium-responsive genes identified from the Affymetrix output were entered into the NCBI Reference Sequence (RefSeq) database. The unique sequence standard of each gene, acquired through the RefSeq accession number, was matched against the human genome assembly at UCSC using the Genome Browser to obtain its mapping information. Based on this information, 1000 bp of promoter sequence was retrieved for each gene. The collective dataset was subsequently analyzed to search for common transcription factor-binding motifs by using the Match program and the TRANSFAC 6.0 transcription factor database. Of the 287 genes analyzed, 113 (39%) contain gut-enriched krüppel-like factor (GKLF) consensus element in their promoter regions. GKLF is a zinc finger transcription factor that is important in controlling cell growth and differentiation. Expression of GKLF has been found to be reduced in prostate cancers compared with normal epithelium (*Cancer Res.*, 60, 6488-6495, 2000). EMSA and Northern analysis showed that selenium treatment resulted in an induction of both the transcriptional activity and the expression level of GKLF. The role of GKLF in regulating the expression of the early selenium-responsive genes is currently being examined. The present study provides a paradigm of how to apply bioinformatics tools to investigate the molecular mechanism of a cancer chemopreventive agent.

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A190 Selenium Affects an Array of Androgen-Regulated Genes and Other Targets Implicated in Prostate Carcinogenesis: Evidence from cDNA Microarray Analysis. Haitao Zhang, Yan Dong, Norma J. Nowak, James R. Marshall, Clement Ip. *Roswell Park Cancer Inst., Buffalo, NY.*

A previous trial showed that selenium supplementation significantly reduced the incidence of prostate cancer. Little is known about whether selenium might interfere with androgen action or modulate the expression of genes implicated in prostate carcinogenesis. The present study examined the cellular and molecular effects of selenium in the androgen-responsive LNCaP human prostate cancer cells. Physiological concentrations of selenium in the form of methylseleninic acid produced a dose- and time-dependent inhibition of growth with this cell line. An arrest at G_0/G_1 phase and a concomitant delay of passage to S phase were not observed until 24 hr. Profiling of selenium-mediated gene expression changes with a custom 3K human cDNA microarray were done after 3, 6, 12, 24, 36 or 48 hr of treatment. A significant reduction of androgen receptor (AR) mRNA was detected. The change in AR expression was verified by real-time RT-PCR as well as Northern and Western analyses. More importantly, the expression pattern of PSA, a key target of AR, was closely correlated with that of AR. The reduction of both AR and PSA occurred as early as 6 hr post-selenium treatment. The decreases were sustained for 24 hr, but their expression levels returned to that of the untreated control upon longer culture. The acute effects of selenium on AR and PSA were therefore independent of cell growth. In order to identify other selenium-modulated AR-targets, we compared our array file with the one generated by DePrimo *et al.* in LNCaP cells exposed to a potent synthetic androgen, R1881 (Genome Biol., 3: research0032.1-0032.12, 2002). Of the 48 genes significantly modulated on both arrays, 16 were oppositely modulated by selenium and R1881. To further investigate whether these genes are direct targets of AR, we retrieved 5000-bp promoter sequence for each gene and searched for androgen response element (ARE) in the promoters. Of the

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