and 166±49 (control group); 0.29±0.31 ($p<0.05$), 1.2±2.5 ($p<0.05$) and 96±43 ($p<0.05$) (VA group); 0.15±0.11 ($p<0.05$), 1.0±0.8 and 106±42 ($p<0.05$) (BC group); 0.39±0.42, 2.1±2.0 ($p<0.05$) and 107±45 ($p<0.05$) (ATRA group); 0.34±0.36, 1.7±2.8 ($p<0.05$) and 61±42 ($p<0.05$) (9CRA). In addition, the hepatic PCNA labeling indexes (%) analyzed by imunohistochemistry (normal adjacent tissue and PNL, respectively) were: 5.3±2.2 and 6.7±2.5 (control group); 1.7±0.7 ($P<0.05$) and 2.4±1.0 ($p<0.05$) (VA group); 2.3±0.8 ($p<0.05$) and 3.0±0.8 ($p<0.05$) (BC group); 3.3±0.6 ($p<0.05$) and 4.1±0.9 ($p<0.05$) (ATRA group); 2.2±0.5 ($p<0.05$) and 2.2±0.9 ($p<0.05$) (9CRA group). No significant differences were observed among the experimental groups in the hepatic apoptotic indexes (normal adjacent tissue and PNL, respectively) as determined by morphological criteria. Therefore, these data indicate that the retinoids and the carotenoid present pronounced chemopreventive activities during hepatocarcinogenesis and suggest that these protective actions could be attributed to an inhibition of cell proliferation but not to an induction of apoptosis. Financial assistance: FAPESP/CNPq/CAPES.

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Emodin inhibits MMPs scretion and invasion in glioblastoma cells

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Emodin (3 methyl-1, 6, 8 trihydroxyanthraquinone), is an inhibitor of the protein tyrosine kinase, has been shown to display a number of biological activities such as antiviral, antimicroviral, immunosuppressive, anti-inflammatory, and anticancer effects. Emodin was shown to suppress HER-2/neu tyrosine kinase activity in HER-2/neu overexpressing human breast and lung cancer cells and can increase the repair of UV- and cisplatin induced DNA damage in human cells. In this report, we investigated the effects and mechanisms of emodin inhibited cell invasion in human tumor cells. Cancer cell invasion requires coordinated processes, such as changes in cell-matrix adhesion, degradation of the extracellular matrix, and cell migration. We found that emodin significantly inhibited invasion of glioma cells through the modified invasion assay. Adhesion of cells to the collagen matrix was also inhibited. Moreover emodin reduced expression of MMP-2 and induced MMP-9 in various tumor cell lines(breast, cervical, prostate, glioma). Both AKT/PKB and MAP Kinase are involved in the modulation of MMP production. Our results demonstrated that emodin inhibits cell invasion by reduction of MMP expression through bolcking FAK, MAP kinase and AKT/PKB pathway and suppression of transcription factor, NF-kB and AP-1. These results suggest that emodin can contribute to the reduction of invasion in tumors. In summary, our results indicate that emodin, a tyrosine kinase inhibitor, can effectively inhibit PMA or hyaluronic acid induced MMPs activation and *in vitro* invasion of glioblastoma cells as well as other cancer cells. These results may have important chemotherapeutic implications for emodin as a anti-invasive and anti-metastatic agent

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Beta-adrenergic, AA-dependent pathways as targets for chemoprevention of pulmonary and pancreatic adenocarcinoma

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Pulmonary adenocarcinoma and pancreatic adenocarcinoma are among the leading causes of cancer deaths. Both cancers are highly resistant to existing preventive and therapeutic approaches. Our data in human cancer cell lines derived from adenocarcinomas of the lungs or pancreas with or without activating point mutations in K-ras indicated that both cancers are regulated by beta-adrenergic receptors that control the release of arachidonic acid (AA). Beta-blockers, inhibitors of cyclooxygenase-2 (COX-2) or 5-lipoxygenase (5-LOX) inhibited the growth of both cancer types irrespective of the presence of ras mutations. Preliminary data indicate cross-activation of the EGF pathway by beta- adrenegic stimulation. Bioassays in hamster models of NNK-induced pulmonary or pancreatic adenocarcinomas revealed strong chemopre- ventive effects of the beta-blocker propranolol, the COX-inhibitor aspirin, or the 5-LOX inhibitor MK886. Our data suggest blockade of beta- adrenergic receptors and the AA-cascade as promising targets for the chemomoprevention of pulmonary and pancreatic adenocarcinoma.

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The chemopreventive activities of farnesol and geraniol in rats submitted to the resistant hepatocyte model of hepatocarcinogenesis involve inhibition of cell proliferation

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Natural occurring isoprenoids found in citric fruits and herbs essential oils have been considered a potential class of chemopreventive agents. Therefore, in this study farnesol (FR) and geraniol (GR) chemopreventive activities were evaluated on preneoplastic lesions (PNL) induced in Wistar rats by the resistant hepatocyte model of hepatocarcinogenesis (initiation with diethylnitrosamine followed by selection/promotion of initiated hepatocytes with 2-acetylaminofluorene and partial hepatectomy). Thus, the animals received by gavage during 8 consecutive weeks FR (25 mg/100g body weight [bw]; FR group), GR (25 mg/100g bw; GR group) or corn oil (CO) (0.25 mL/100g bw; control group). One hour before sacrifice the rats were injected with 5-bromo-2-deoxyuridine (BrdU). The macroscopic examination of the livers (incidence and average number of PNL, respectively) showed: 100% and 42±46 (control group); 13% and 1±3 ($p<0.05$) (FR group); 42% and 18±45 (GR group). Moreover, the morphometric analysis of GST-P positive PNL (area [mm^2], % of the section area occupied by PNL and number of PNL/cm^2, respectively) revealed the following: 0.18±0.33, 10.0±7.4 and 50±13 (control group); 0.09±0.17 ($p<0.05$), 2.8±3.6 ($p<0.05$) and 34±22 (FR group); 0.11±0.25 ($p<0.05$), 5.1±2.9 and 53±36 (GR group). In addition, the plasmatic (mg/dL) and hepatic (mg/g) total cholesterol levels evaluated by enzymatic and HPLC methods, respectively, were: 64±7 and 3.14±0.2 (control group); 55±8 ($p<0.05$) and 3.07±0.2 (FR group); 69±8 and 3.12±0.2 (GR group). Furthermore, BrdU labeling indexes (%) analysis by imunohistochemistry in the livers of the animals from the control, FR and GR groups (normal adjacent tissue and PNL, respectively) showed the following: 1.2±0.8 and 1.8±0.7 (control group); 0.4±0.7 ($P<0.05$) and 0.5±0.7 ($p<0.05$) (FR group); 0.5±0.8 and 0.6±0.8 ($p<0.05$) (GR group). Therefore, these data indicate that both isoprenoids (farnesol and geraniol) present pronounced chemopreventive activities during hepatocarcinogenesis and suggest that these protective actions could be attributed, at least in part, to their inhibitory effects on cell proliferation. Financial assistance: FAPESP(00/00918-8)/CNPq/CAPES.

Differentiation

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Pathway pathology: how to identify signaling pathways in mouse models of human breast cancer

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Human mammary cancer is frequently associated with a mutational activation of the ErbB (HER-2) signal transduction pathway. In contrast, "spontaneous" mouse mammary tumors are associated with either Wnt or Fgf signaling and do not resemble human breast cancer. Using examples of genetically engineered mice from these signaling pathways from the UCD Mutant Mouse Pathology Laboratory, we have studied the histological characteristics of mammary tumors arising in these mice. We found that the studied pathways induce tumors with unique, identifiable histomorphologies. These observations are the foundation for Pathway Pathology. Phenotypical effects of ErbB/Ras pathway activation were studied in tumors transgenic for ErbB2, mutant forms of ErbB2, PyV-mT (a viral protein substitute for ErbB2), Ras, and bigenics with both ErbB2 and another transgene. Mammary tumors caused by overexpression of these transgenes tend to resemble human Ductal Carcinoma in Situ, are solid, not metaplastic, lose myoepithelial differentiation, have scanty stroma, but frequently have an invasive growth. Examples studied for Wnt pathway activation include: Wnt-1, Wnt-10b, Adenomatous Polyposis Coli gene, Gsk-3β, Casein kinase II, and β-Catenin. The Wnt pathway mammary tumors resemble the classical, virus-induced, Type A, B and P tumors, and are more heterogeneous than the ErbB/Ras tumors. However, Wnt tumors share common histomorphologic characteristics, which allow the distinction from the ErbB/Ras tumors: organization around central ducts, presence of acinar, glandular, papillary, squamous or pilar components, retained myoepithelial differentiation, dense stroma, and expansile growth. Some genotypes predispose for spindle cell