membrane steroid agonists modify APRIL transcription levels. Conclusions: Our data show, for the first time, an autocrine secretion of APRIL in breast cancer cells, strongly associated with loss of differentiation and metastatic potency, indicating the emerging role of this TNF-related cytokine in breast cancer biology. The regulatory effect of membrane agonists on APRIL gene regulation reflects another aspect of membrane steroid signaling, providing new insights in the hot link between inflammation and breast cancer promotion.

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PTEN deletion detected using dual-color FISH in esophageal squamous cell carcinoma correlates with poor prognosis

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Background: Esophageal squamous cell carcinoma (ESCC) is the most frequent histological type of cancer in this organ, being the sixth neoplasia in frequency in Brazil. ESCC is associated with poor prognosis, showing high mortality rates. It is important to know the prognostic factors that can help the choice of more appropriate surgical approach and then improve the survival of these patients. The tumor suppressor gene PTEN (phosphatase and tensin homolog deleted on chromosome 10) is a member of protein tyrosine phosphatase family that can inhibit cell proliferation, survival and growth by inactivating PI3-kinase-dependent signaling. Mutations of PTEN gene have been described in a variety of tumor types, but there are few studies in ESCC. The aim of this study is analyze the presence of PTEN deletion through Fluorescent in situ Hybridization (FISH) in cases of ESCC and its correlation with tumor prognosis.Material and Methods: 70 surgical resections of ESCC cases were performed in two Tissue Microarray (TMA) paraffin blocks spotted in duplicate. All medical records were reviewed. Dual-color FISH reactions were carried out using commercially available probe for PTEN locus (Vysis) and for centromere of chromosome 10 (Vysis). In each case, 100 non-overlapped, interphase tumor nuclei were evaluated. Hemizygous deletion of PTEN was defined as >20% of tumor nuclei with one PTEN locus signal and presence of CEP10 signals. Homozygous deletion was characterized as lack of both PTEN locus signals, but presence of CEP10 signals in >30% of tumor cells.Results: Our study showed that 41 (58,6%) of 70 cases analyzed showed PTEN deletion, being 38 (54,2%) hemizygous deletion and 3 (4,2%) homozygous deletion. It was not possible to perform the statistical analysis to verify the association between the FISH results and clinicopathological findings. According to univariate analyses, the variables gender (p=0,002), lymph nodal metastasis (p

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Pro-apoptotic effects of streptochlorin isolated from Streptomyces sp. in human leukemic U937 cells

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Streptochlorin is a small molecule produced by marine Streptomyces sp. (strain 04DH110) that is known to have anti-angiogenic and anti-cancer properties. However, the mechanism by which streptochlorin exerts is effects is not well understood. In this study, we investigated the pro-apoptotic effect of streptochlorin in human leukemic U937 cells. Streptochlorin treatment resulted in concentration- and time-dependent growth inhibition of U937 cells by inducing apoptosis, as evidenced by the formation of apoptotic bodies, DNA fragmentation and the accumulation of cells in the sub-G1 phase. The increase in apoptosis that was induced by streptochlorin was correlated with down-regulation of the anti-apoptotic Bcl-2 expression, up-regulation of pro-apoptotic Bax and FasL, a decrease in the mitochondrial membrane potential (MMP, $\Delta\psi_m$), activation of caspases and degradation of poly-(ADP-ribose) polymerase (PARP) and phospholipase C (PLC)-g1 protein. Both the cytotoxic effects and apoptotic characteristics induced by streptochlorin were significantly inhibited by z-DEVD-fmk, a caspase-3 inhibitor, which demonstrates the important role that caspase-3 played in the observed cytotoxic effects. Furthermore, Bcl-2 overexpression significantly reversed the streptochlorin-induced growth inhibitory effects via inhibition of the MMP collapse and caspases activation and effectively attenuated the apoptotic response to streptochlorin. However, the elevated levels of FasL expression induced by streptochlorin were not reduced by Bcl-2 overexpression. Taken together, these findings demonstrate that the pro-apoptotic effect of streptochlorin is mediated through activation of caspases and mitochondria in U937 cells. [This research was supported by a grant (M2007-03) from Marine Bioprocess Research Center of the Marine Bio 21 Center funded by the Ministry of Maritime Affairs & Fisheries, Republic of Korea.]

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Inhibition of invasion and induction of apoptosis by anthocyanins isolated from Vitis coignetiae Pulliat in HCT116 colon cancer cells

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Many edible plant metabolites are known to be useful as cellular anti-oxidants. Anthocyanins belong to a class of flavonoids, exhibiting anti-oxidant and anti-inflammatory actions as well as a variety of chemotherapeutic effects. However, the underlying mechanisms of its action are not completely understood in anti-cancer effects. In this study, we investigated if the anthocyanins isolated from meoru (Vitis coignetiae Pulliat) exerted anti-proliferative, anti-invasive and apoptotic effects on human colon adenocarcinomaHCT116 cells. It was found that the anthocyanins could inhibit cell growth by 50% at the concentration of 60 μg/ml for 48 h. Flow cytometric analysis showed that the anthocyanins treatment increased the sub-G1 population in a dose-dependent manner, which is closely related to modulation of Bcl-2 and inhibitor of apoptosis proteins (IAPs) family expression. Consequently, anthocyanins treatment induced the proteolytic activation of caspases and degradation of poly (ADP-ribose) polymerase (PARP). Furthermore, anthocyanins significantly inhibited the cell migration and invasion of HCT116 cells. Also, the inhibitory effects of migration and invasion by anthocyanins were associated with up-regulation of E-cadherin expression, and down-regulation of Snail, matrix metaloprotenase-2 (MMP-2), MMP-9 and claudins. Taken together, these observations indicate that the anthocyanins have anti-proliferative and anti-invasive effects, and may induce the apoptosis through the activation of mitochondrial pathway and inhibition of anti-apoptotic proteins. This study provides evidence that the anthocyanins isolated from meoru might be useful in the treatment of human cancer cells.

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Genetic instability of FADD-deficient mouse cells

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We used fibroblast cultures from the FADD-deficient mouse embryos, which were originally constructed by T.W. Mak (Toronto, Ont.) to assess directly the role of FADD, a death receptor-associated protein, in cells responses to UV radiation.

These FADD-deficient fibroblasts showed much increased growth rate compared with the wild-type homozygous cells. However, the FADD-deficient fibroblasts showed the same sensitivity to UVC radiation as the wild type homozygous fibroblasts measured by MMT test. There was no difference between repair activity of UV-induced DNA damages products in the FADD-deficient and proficient cells, either. However, delay of entering S phase after UV-irradiation was reduced in the FADD-deficient cells, indicating some abnormality in the checkpoint function of the cell cycle in these deficient cells. We further analyzed changes of p53 sequences in the FADD-deficient and wild-type cells. Genomic DNA was analyzed by allele-specific polymerase chain reaction (AS-PCR) for CC to TT mutation at codons 154-155 and 175-176 in exon 5 and for C to T mutations at codons 270 and 275 in exon 8 0f the p53 gene. The mutant-specific forward primer was used for each mutation. The reverse primers for amplification of mutations were not mutant-specific. Allele-specific PCR detection of p53 in genomic DNA were analyzed by gel electrophoresis. The results showed the high frequency of changes in the mutant-specific primer for codon 270 amplified 134-base pair product from FADD deficient cell DNASs. Although frequencies of UV-induced mutations were not different between the FADD-deficient and wild-type cells, distributions and spectrum of base-substitution mutations at the p53 were different.