CB-P13

CHLORPYRIFOS PRODUCES DISSIMILAR EFFECTS ON PROLIFERATION IN BREAST CANCER CELLS

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A large body of literature suggests that environmental chemicals are involved in breast carcinogenesis. It has been postulated the use of the organophosphorus chlorpyrifos for replacing the current pesticide for fruit-bearing trees treatment in Alto Valle de Rio Negro and Neuquen. The aim of the present study was to evaluate the effect of chlorpyrifos on cell proliferation of human breast cancer cell line, MCF-7. Proliferation was evaluated by clonogenic assay and bromodeoxyuridine (BrdU) incorporation; cell viability by MTT assay. Reactive oxygen species (ROS) were determined using DCF fluorescent staining and flow citometry. Protein expression was assessed by Western blot. Our results indicate that high concentrations of chlorpyrifos (50 μM) decreased 40% clonogenic proliferation and 18% cell viability. The inhibitory effect on proliferation was associated to an increase of 32% in the content of ROS and 48% p27 protein expression. On the other hand, exposure of cells to low concentrations of chlorpyrifos (50 nM) stimulated BrdU incorporation in 88%. This effect was related to an enhanced expression of proliferating cell nuclear antigen (PCNA) and cyclin E. We conclude that chlorpyrifos modulates proliferation in a dose dependent way, increasing proliferation at low doses while decreasing it at high concentrations.

CB-P14

ROLE OF PTH AND PTHrP IN THE REGULATION OF CELL CYCLE IN COLON ADENOCARCINOMA CELLS

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Parathyroid hormone (PTH) functions as a major mediator of bone remodeling and as an essential regulator of calcium homeostasis. Parathyroid hormone-related protein (PTHrP) was initially identified through its role in humoral hypercalcemia of malignancy and is able to interact with PTH receptor type 1. In this study, we investigated the role of PTH and PTHrP in the regulation of the cell cycle in human Caco-2 intestinal cells. First, the nuclei were stained with propidium iodide and the DNA content was measured using a flow cytometer. The results revealed that PTH treatment (10^{-8} M, 24 h) increases the number of G0/G1 phase cells and diminishes the number of S phase cells respect to control. In addition, analysis by western blot showed that the hormone induces the expression of the inhibitory proteins p27 and p15 and diminishes the expression of cyclin D1 and D3. However, the amount of p21 was not different in the absence or presence of PTH. By contrast, and although they share the same receptor, there was no change in the expression of these proteins after exposure of Caco-2 cells to PTHrP (10^{-8} M). Taken together, our results suggest that PTH induces changes in the expression of proteins involved in cell cycle regulation and produces G0/G1 phase arrest of Caco-2 intestinal cells.

CB-P15

MANNOSE-6-PHOSPHATE/INSULINLIKE GROWTH FACTOR II RECEPTOR IN DIABETIC RAT MAMMARY CARCINOGENESIS

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We developed mammary tumors in normal and diabetic rats (streptozotocine induced diabetes) by three ip. injections of N-Nitroso-N-Methylurea (NMU) at 50, 80 and 110 days of animals life. The aim of this work was to study the expression of insulin-like-II receptor (IGF-IIR) in mammary gland during carcinogenesis in relation to proliferation markers PCNA and Ciclin D1. Four groups of rats were employed: 1) control; 2) NMU-injected; 3) diabetic; 4) diabetic-NMU injected. Mammary tissue was processed at 60, 90, 120 and 180 days of animal life.
IGF-IIR expression, determined by inmunoblot and immunohistochemistry, was high in group 1 and 3 at all times while in group 2 the expression was reduced with mammary tissue transformation and was significant since 90 days of life. In diabetic-NMU injected animals only a very slight decrease in IGF-IIR expression was evident. Proliferation markers, PCNA and Ciclin D1 expression, were inversely correlated to IGF-IIR expression. When tumors were analyzed, IGF-IIR expression was clearly higher in those developed in diabetic animals. Also, PCNA and Ciclin D1 expression were lower and related to a slower growth rate. These malignant lesions showed a more differentiated histological pattern and longer latency periods than tumors of non diabetic rats. Our results are in correlation with the idea that IGF-IIR acts as a tumor suppressor gene.

CB-P16

EFFECT OF OLIGOELEMENTS AND *Lachesis muta* ON RAT COLONIC CHEMICAL CARCINOGENESIS

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We have previously reported the antitumoral effect of the combination of oligoelements Se, Zn and Mn (4 μg/ml each, Merck) plus Lachesis Muta (4 ng/ml whole venom, Sigma Co) (O-Lm) on experimental mammary and pancreatic carcinomas (Int J Cancer, 2002; Anticancer Res 24:3434-35, 2004; Biocell 29(Supl)102,2005. In the present work we investigated whether O-Lm could prevent rat colonic carcinogenesis induced by 1,2-dimethylhydrazine (DMH).
Two month-old male rats (n=40) received 20 subcutaneous (s.c.) weekly injections of DMH (30 mg/Kg). Half of the animals received a daily s.c. O-Lm injection (0,5 ml) starting 10 days before the first DMH administration; this treatment continued during the entire experimental period. Animals were sacrificed at 12, 18, 21, 24, 28 weeks and histopathological (H&E and PAS staining) and immunohistochemical analyses of PCNA, Ciclin E, Bax, Bcl-2, and antioxidant enzymes were performed in complete colonic mucosa. Results show that O-Lm treatment significantly reduced the number of colonic DMH-induced tumors. This effect was associated with a decrease in PCNA expression, a modulation of pro and antiapoptotic proteins and antioxidant enzymes along the carcinogenic process.
We conclude that O-Lm is a preventive agent of colon carcinogenesis in this experimental model through the modulation of the apoptotic and proliferation process.