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A29

EFFECT OF ALLOPREGNANOLONE, A PROGESTERONE METABOLITE, ON HUMAN OVARIAN CANCER CELL LINES PROGRESSION: POTENTIAL USE AS THERAPEUTIC TOOL

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Ovarian cancer is one of the most common cause of gynecologic cancer death. Allopregnanolone (ALLO), a progesterone (P4) metabolite, modifies ovarian physio-pathological processes. The effects of progesterone, its precursors and derivatives have been extensively studied in breast cancer. Progesterone and the 5α derivatives are known to have a protective effect, the 4- pregnenes have the opposite effect. While in ovary very little is known about its actions. Changes in ALLO levels during estrous cycle or under stress situations can generate several alterations in ovarian development. We reported the first evidence that ALLO induces ovarian morpho-physiological changes altering proliferation, apoptosis, and angiogenesis. Epidemiologic and *in vitro* studies have shown controversial information about P4 effects in cancer. The effect of P4 metabolites over ovarian cancer is relevant and require more deep trials due to it could be involved on cancer progression. Then, we first investigated biological behavior of culture cells in proliferation, apoptosis, clonogenic capacity and migration experiments in two human ovarian cancer cell lines IGROV-1 and SKOV-3. Two cell lines were exposed to increasing concentrations of both drugs, from physiological, stress and pharmacological concentrations (10^{-11} to 10^{-5} M) for 72 h. Proliferation was analyzed by MTT and Ki67 expression. Apoptosis was measured by immunocytochemistry of cleaved caspase 3. Clonogenic capacity was evaluated by counting colonies. Migration was analyzed by wound assay. ALL increased proliferation and Ki67 expression respect to control on IGROV-1 cells, while expression of cleaved caspase 3 did not change in any cell line studied. In IGROV-1 clonogenic capacity was also increased by ALLO treatment. Both steroids, P4 and ALLO, increased IGROV-1 migration in a concentration dependent manner. None of the steroids modified SKOV-3 biological behavior. This is the first evidence that ALLO affects biological process that can affect tumor development of human epithelial ovarian cancer. The regulation of progesterone and allopregnanolone steroideogenesis and their molecular mechanisms of action could be considered as potential therapeutic tools in ovarian cancer. In conclusion, ALLO significantly increase malignant proliferation in human epithelial ovarian cancer, then a pharmacological inhibition of ALLO cyclic elevation could be a potential anti-cancer tool.

POSTER PRESENTATIONS

GENERAL, CELLULAR AND MOLECULAR BIOLOGY

A30

EFFECT OF BOTULINUM NEUROTOXINS FROM MENDOZA OF *Clostridium botulinum* STRAINS ON CYTOSKELETAL PROTEINS OF MAMMARY TUMOR CELLS

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The botulinum neurotoxin serotype A (BoNT A) produced by *Clostridium botulinum*, which causes botulism, is used for the treatment of multiple neurological diseases and its therapeutic action against cancer is currently being evaluated. In previous studies, we have shown that BoNT A from autochthonous soil strains (Su) have different properties than the reference A Hall strain. Among these, its molecular structure, its enzymatic activity against brain SNARE proteins and its greater specific toxic activity (AE) stands out. In cells from human mammary carcinoma (MCF-7) treated with BoNTs for 45 min, we found a marked effect on the expression of cytoskeletal proteins. Therefore, in this work, we delve into the study of the action of autochthonous BoNTs A and prototype A Hall on the distribution of actin and tubulin in these cells. Native forms of autochthonous BoNT (Su strains 1935 and 1891, Tupungato) and prototype A Hall were purified by saline precipitation. Their AE values (LD_{50}/mg protein) were established, and their electrophoretic characteristics were evaluated under non-denaturing conditions. 250 LD_{50} of the BoNTs were incubated to MCF-7 cell cultures for 10 or 25 min. Later, the cells were fixed and processed for indirect immunofluorescence with the use of specific antibodies that recognize tubulin or actin. The samples were visualized by fluorescence microscopy. At the two times evaluated, the three types of BoNTs produced a marked redistribution of the actin cytoskeleton, patch form, on areas coinciding with the plasma membrane. Tubulin was redistributed to multiple areas with high signal density at 10 min of incubation only in the presence of BoNT 1891. At 25 min of incubation, the cells treated with BoNTs 1891 and 1935 showed this effect, while in those incubated with A Hall, the distribution of these proteins was not modified. The notable alterations in the distribution of components of the tumor cell cytoskeleton by BoNT from native strains of Mendoza soils open new perspectives for therapy against solid tumors.