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Evidences from our group demonstrated the emergence of cellular senescence process as a growth control mechanism during the progression of estrogen-induced pituitary tumors. Also, estrogen exerts a modulatory action on pituitary cells proliferation. Considering the preponderant role of NF-kB (p65) in cellular senescence and points of convergence between ERa and NF-kB signaling pathways in cell cycle control, we evaluate the contribution of the interaction between these two proteins in the pituitary senescence in experimental pituitary tumors. Wistar adult male rats were implanted subcutaneously with silastic capsules containing estradiol benzoate (30mg) for 10, 20, 40 and 60 days (E10-60). The control group was implanted with empty capsules. Subsequently, ERa:NF-kB immunoprecipitation was performed at the different stages of tumoral development. NF-kB and IkBa levels were also determined from nuclear and cytosolic fractions by Western blot. The ERa:NF-kB co-localization was analyzed by immunofluorescence (IF) and transmission electron microscopy (TEM). Statistical analysis: ANOVA-Fischer test ($p<0.05$). During the course of estrogen-induced pituitary tumoral development, a significant ERa:NF-kB association was detected, with a marked interaction at E10 and E60, result that was corroborated by IF and TEM. Also, a significant increase in NF-kB and IkBa protein levels in the cytosolic compartment was detected. Interestingly, a substantial increased in the NF-kB nuclear levels was evidenced at E20 and E40 compared to those observed at E10 and E60. Probably, ERa recruits NF-kB at the cytoplasmic compartment in order to inhibit their function as a transcription factor and thereby modulate cell senescence-associated molecular mechanisms during the progression of the experimental pituitary tumor. These results suggest a cross-talk between NF-kB and ERa signaling pathway that may lead to the emergence of cellular senescence, thus contributing to the control of the cell growth.

718 (813) **SIGNS OF ALTERATIONS IN THE MITOCHONDRIAL DYNAMIC AND OXIDATIVE STRESS IN THE SENESCENCE PROCESS DURING THE DEVELOPMENT OF ESTROGEN-INDUCED PITUITARY TUMORS**

Ezequiel Grondona[1], María Eugenia Sabatino[1], Bethania Mongi Bragato[1], Lucía Carreño[1], Liliana Sosa[1], Juan Pablo Petiti[1], Silvina Gutiérrez[1], Alicia Torres[1], Alexandra Latini[2], Ana Lucía De Paul[1].

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Evidence of cellular senescence process during in vivo estrogen-induced pituitary tumor development was recently described in our laboratory. Since mitochondrial metabolism and dynamic are targets of estrogen action and senescence is considered a stress response triggered by different factors including oxidative stress; we evaluate the effects of estrogen in vivo on mitochondrial function and dynamics in experimentally

induced proliferative lesions. To induce pituitary tumoral development, Wistar male rats were exposed to estradiol benzoate (30mg) implanted subcutaneously in silastic capsules for 10, 20, 40 and 60 days (E10-60). Control group: animals treated with empty capsules. The morphological and morphometric mitochondrial analysis was evaluated by transmission electron microscopy; ROS production and mitochondrial membrane potential was determined by flow cytometry. Mfn1, Mfn2, OPA-1, Drp1; 8OHdG and Nrf2 protein expression were assessed by immunohistochemistry and western blot. Statistical analysis: ANOVA-Fischer test ($p <0.05$). Increases in mitochondrial number accompanied by a circular and less elongated morphology was observed at E10. The gradual increase of mitochondrial fusion proteins expression: Mfn1, Mfn2 and OPA-1 and the reduction of Drp1 fission protein levels, suggested the prevalence toward the mitochondrial fusion. A significant increase in ROS production and changes in mitochondrial membrane polarity, were signs of oxidative stress. The increase of nuclear 8OHdG expression at the beginning of tumoral development and increases in Nrf2 levels revealed the activation of defense mechanisms against the estrogen-induced proliferative injury. These data suggest that alterations in the mitochondrial dynamic and oxidative stress detected in early stages of estrogen-induced pituitary tumor development could be responsible for the emergence of senescence as a regulatory mechanism of cellular growth.

719 (881) **DEHIDROEPIANDROSTENEDIONE MODULATES CELLULAR EVENTS INVOLVED IN VASCULAR REPAIR**

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In recent years dehidroepiandrostenedione (DHEA) has emerged as a promising alternative for hormone replacement therapy due to its ability to act as a precursor for local formation of active steroids. Maintenance of vascular health depends mainly on the prevention of vascular injury and the promotion of vessel remodeling (angiogenesis). Endothelial cells (EC) migration and proliferation, and the expression of endothelial factors that enhance EC adhesion to subendothelium (uPA and tPA) are crucial events in new vessel formation. In this study we evaluated the effects of DHEA on processes involved in the initiation of vascular lesions (platelet adhesion and aggregation) and in angiogenesis. We demonstrated that EC treatment with 20nM DHEA produces an inhibition on platelet adhesion to endothelium (24h - 25%below Cont $p<0.05$), and decreases endothelium dependent platelet aggregation (60min - 15%below cont $p<0.05$) in a nitric oxide dependent manner, since preincubation with NAME annulated this effect ($p<0.01$). EC proliferation studies (MTT assay) showed that 24h treatment with DHEA stimulates cell growth (32, 22 and 12% above Cont 2, 20 and 200nM DHEA $p<0.05$). Indeed, using wound healing assays, we found that the steroid also promotes cell motility (9±2, 25±8 Cont, 20nM DHEA migrating cells/field $p<0.01$). The expression of uPA, tPA and androgen receptor (AR) was measured by inmunoblot. To that end, EC were treated for 12 to 48h with 20 or 200nM DHEA. The steroid enhances the expression of both factors (30-80% above control $p<0.05$). The androgen receptor expression was also increased, suggesting that DHEA mechanism of action could involve AR. Finally, in rat aortic ring angiogenesis assays, we observed that DHEA treatment promotes EC sprouting and capillary like tube formation (30% above control, $p<0.05$). The presented results show that DHEA exerts a direct action on EC, contributing to the prevention of vascular injury and promoting angiogenesis

720 (897) **IMPORTANCE OF HORMONAL OVARIAN FOLLICULAR FLUID LEVELS IN AN ASSISTED FERTILIZATION PROGRAM: ROLE OF THYROID HORMONES AND ESTRADIOL**

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Follicular fluid (FF) is the microenvironment in which the follicles develop and the oocytes mature. Hormonal composition influences oocyte quality and maturity, main parameters for assisted fertilization outcome. Thyroid hormones in the FF would have a positive role during folliculogenesis and ovulation.

Aim: to analyze the role of thyroid hormone and estradiol in the FF in relation to oocyte maturation rate (OMR) in women recruited for assisted fertilization procedure.

Subjects and methods: 51 women (29 to 42 years) without autoimmunity or medication affecting thyroid function were evaluated after a controlled ovarian stimulation protocol. In the remnant FF