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Deregulation of cellular energetics has become one of the hallmarks of cancer evidenced by the numerous connections between signaling pathways that include oncoproteins and key metabolic enzymes. Heme Oxygenase-1 (HO-1) is a cellular homeostatic regulator counteracting oxidative and inflammatory damage. We previously showed that HO-1 has an antitumoral activity in prostate cancer cells. It inhibits cell proliferation, migration, tumor growth and angiogenesis. The aim of this project was to further study the role of HO-1 on the energetic metabolism of prostate cancer cells.
In earlier studies, we demonstrated a significant reduction in ATP production and oxygen consumption rate in PC3 cells (derived from a metastatic prostate tumor) after treatment with hemin (inducer of HO-1 expression and activity) 80 μM for 24h. These results confirmed a negative regulation on the metabolic rate.
In this work, in order to further analyze the regulation of cell metabolism by HO-1, we studied glucose uptake in PC3 cells. We found lower glucose uptake in cells treated with hemin (20.32 vs 3.52 fmol/cell/min; $p<0.0001$). We also inferred the number of mitochondrias by the quantification of mtDNA by qPCR and analyzed mitochondria integrity by flow cytometry using the TMRE dye. Neither the number nor integrity showed significant changes as a result of the hemin treatment. In addition, we analyzed the expression of key genes involved in metabolic pathways and cancer progression. HO-1 induction downregulated *LDHA* (FC=0.5; $p<0.05$) while it did not alter the expression of *PKM2*, *ACO2* and *PDHB*.
In conclusion, our results showed that HO-1 might be involved, at least in part, in the reprogramming of the metabolic state of PC3 cells, which might favor the establishment of a less aggressive phenotype of the disease.

271. (289) **STUDY OF THE ROLE OF P300 IN THE DEVELOPMENT AND PROGRESSION OF BREAST CANCER**

María Eugenia Fermento, Florencia Mariani, Eliana Alonso, Norberto Ariel Gandini, Josefina Guevara, Silvina Grioli, María Julia Ferronato, Georgina Pamela Coló, Marilina Mascaró, María Marta Facchinetti, Alejandro Carlos Curino
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Breast cancer (BC) is a heterogeneous disease with many subtypes that has different treatment responses and clinical outcomes, suggesting the need to find new molecular markers. We have previously shown that pharmacological inhibition of p300 displays antitumor activity in LM3 and MDA-MB-231 BC cell lines and in their respective murine models. Through genetic silencing of p300 in MDA-MB-231 cells we also demonstrated a decrease in cellular viability, migration, invasion and adhesion. We also showed that p300 silencing decreases cellular viability in LM3 cells and reduces the primary tumor growth in its syngeneic murine model. However, the role it plays in the metastatic process remained unknown. Therefore, in this work we aimed to study the effect of genetic silencing of p300 on tumor progression and invasion in LM3 cells and its syngeneic murine model. We obtained LM3 cells stably-overexpressing a shRNA for p300 (LM3-p300NEG) or its control plasmid (LM3-CTRL). The reduction in p300 levels was confirmed by RT-qPCR. We observed reduced cellular migration (wound healing), invasion (transwell with matrigel), adhesion (adhesion to the substrate) and an increase in the levels of E-cadherin and ß-catenin (WB) in LM3-p300NEG compared to LM3-CTRL ($p<0.05$). In the murine model we observed significant reduction in the tumor burden and in the number of lung metastases in mice injected with LM3-p300NEG compared to mice injected with LM3-CTRL ($p<0.05$). In the primary tumors belonging to LM3-p300NEG-inoculated mice, an increase in the expression of E-cadherin, Elf5, ß-catenin and a decrease in p300 were detected when compared to LM3-CTRL-inoculated mice (IHQ, $p<0.05$). We also observed nuclear and cytoplasmic localization of ß-catenin in LM3-CTRL tumors compared with LM3-p300NEG tumors in which only cytoplasmic localization was observed. In conclusion, these results show a protumor activity of p300 in BC, carried out at least in part by modulating tumor invasion, migration and adhesion.

272. (303) **INTEGRIN-SPECIFIC ACTIVATION OF RHO GTPASES, THEIR ROLES IN MECHANOSIGNALLING AND CANCER**

Georgina Pamela Coló[1], Raquel Haga[2], Lucia Fernández-Chavés[1], Eliana Alonso[1], Norberto Ariel Gandini[1], María Eugenia Fermento[1], Josefina Guevara[1], Marilina Mascaró[1], María Julia Ferronato[1], Silvina Grioli[1], María Marta Facchinetti[1], Alejandro Carlos Curino[1], Reinhard Fässler[2]
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Mechanotransduction is mediated by the integrin family of cell adhesion receptors. Integrins bind cell extracellular matrix proteins and connect to the F-actin cytoskeleton and non-muscle-myosin inside the cells. Using genetically engineered cells, biochemical assays, in combination with mass spectroscopy (MS), traction force microscopy and micropatterns, we observed that α5β1-integrin expressing cells promote the formation of small nascent adhesions, low RhoA activation and high force, while αVβ3-integrin expressing cells showed large focal adhesions connected to contractile stress fibers (SFs), resulting in high RhoA but low force. To further analyze pKO-cells phenotypes, we looked for specific RhoA activators (GEFs). We performed a MS-proteomic analysis and amongst the interesting hits was GEF-H1, together with biochemical assays we observed that GEF-H1 activation is dependent on a specific integrin-class suggesting that integrins may activate specific GEFs during adhesion, migration and invasion. Recent studies have also shown that an increase in GEF-H1 expression correlates with an increase in tumor progression and metástasis. In addition, GEF-H1 is involved in the cross-talk between microtubules and the actin cytoskeleton. Our data shows that GEF-H1 is localized in the cytoplasm and more active in αVβ3-cells when compared to α5β1-cells, where GEF-H1 is in an inactive state bounded to the microtubules. Similar results we observed in breast cancer cells depending their invasiveness and the integrin-class-expression. These results could explain the increase in SFs formation in αVβ3-cells and RhoA activation. GEF-H1 can be released to the cytoplasm either by microtubule depolymerization or by protein phosphorylation. A phosphoenrichment-label-free MS analysis revealed that GEF-H1 is highly phosphorylated in αVβ3-cells. Furthermore, using integrin-tail pull-down and MS assay, we observed that GEF-H1 binds to β3-integrin tail. These results show for the first time that GEF-H1-RhoA activation is αVβ3-integrin dependent and it can mediate the signaling involved in controlling cell structure, force generation, migration and invasion.

273. (284) **TNF CONTRIBUTES WITH RAC3-INDUCED MALIGNANT TRANSFORMATION**

Mileni Soares Machado, Laura Panelo, María Cecilia Lira, Francisco Damián Rosa, Gabriela Inés Marino, María Fernanda Rubio, Alejandro Urtreger, Mónica Alejandra Costas
Instituto de Investigaciones Médicas Dr. Alfredo Lanari (IDIM), UBA - CONICET

RAC3 is a coactivator of steroid receptors and transcription factors and an important oncogene in tumor development. We have previously demonstrated that inflammatory cytokines increase the RAC3 expression and that high levels of this molecule could transform non-tumor cells into cancer stem cells. The aim of this work was to investigate if the inflammatory cytokine TNF could contribute to RAC3 transforming effect, maintaining or increasing stem prop-