Abstract/Resumen: The loss of muscle mass and strength with aging, sarcopenia, is a prevalent condition among the elderly, associated with skeletal muscle dysfunction, enhanced muscle cell apoptosis and mitochondrial dysfunction. We have previously demonstrated that testosterone (T) protects against H_2O_2-induced apoptosis in C2C12 muscle cells, at different levels: morphological, biochemical and molecular. However, the role of T and its receptor at mitochondrial level is not well understood. Therefore, here we investigated the impact of physiological concentration of T on mitochondrial gene expression in C2C12 skeletal muscle cells. We found that T caused a significant increase in mRNA expression of genes encoded by mitochondrial DNA, namely NADPH dehydrogenase subunit 1 (ND1) and subunit 4 (ND4), cytochrome b (CytB), and cytochrome c oxidase subunit 1 (Cox1) and subunit 2 (Cox2) in skeletal muscle cells. In addition, gene and protein expression of the nuclear respiratory factors 1 and 2 (NRF1 and NRF2) and mitochondrial transcription factors A (Tfam) and B2 (TFB2M), key regulators of mitochondrial transcription and biogenesis, were also increased after T treatment, being the main regulator of mitochondrial fusion, OPA1, incremented as well. Of relevance, the simultaneous treatment with T and the androgen receptor antagonist, Flutamide, reduced these effects. The actions of the hormone observed were totally opposite to H_2O_2-oxidative stress induced treatment, which significantly reduced mitochondrial gene expression. Computational analysis revealed that mitochondrial DNA contains specific sequences, which the androgen receptor could recognize and bind, probably taking place thus, a direct regulation of mitochondrial transcription by the receptor. These findings indicate that androgen plays an important role in mitochondrial gene expression and biogenesis in skeletal muscle.

0607 - GLOBAL DNA METHYLATION LEVELS ANALYSIS IN A SERIE OF HEMATOLOGICAL, BREAST AND COLORECTAL CANCER SAMPLES FROM ARGENTINA

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Abstract/Resumen: Unlike their normal counterparts, tumor cells exhibit highly variable CpG methylation levels in a large proportion of the genome, which can lead to malignant cell transformation through multiple pathways. This prompted us to assess the extent of LINE1 methylation, a surrogate marker of global DNA methylation, of samples derived from controls and cancer patients from Argentina. Preliminary DNA methylation results from selected samples were replicated in a large serie of 146 controls (blood) and various cancer types: 112 hematological cancer (HemCa), 70 colorectal cancer (CRC) and 68 breast cancer (BrCa) samples. Further, we evaluated correlation with biological, clinical and demographic features. Blood samples were available in all cases, and for solid tumors paired tumoral/non-tumoral adjacent tissues (T/N) were available too. LINE1 methylation level was analyzed by MS-MLPA method. HemCa cases showed statistically significant higher LINE1 methylation level ($p<0.001$) compared to controls (mean= 0.93 and 0.84, respectively). This variation could be a consequence of chemotherapy. Methylation status in blood (0.86) and N tissue (0.87) from BrCa cases did not differ from controls, while levels in T tissue (0.88) were significantly higher than controls ($p<0.05$). No differences between N and T tissues were found. CRC cases showed hypomethylation for LINE1 when comparing T (0.81) to blood (0.87) or N tissues (0.88), reaching statistical significance of $p<0.05$ and $p<0.001$, respectively. This is in line with reported results. We found a negative correlation between age and methylation level in controls (-0.17, p= 0.04), and BrCa T tissue (-0.33, p= 0.03). Finally, no relevant associations between global methylation and mitochondrial genome variation (copy number and ancestry) were found for controls and HemCa sample sets. LINE1 methylation analysis in samples from lung, ovarian, pancreatic and skin cancers are ongoing.

0659 - RELEVANCE OF GLUCOCORTICOID RECEPTOR IN ACUTE MYELOID LEUKEMIA

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Abstract/Resumen: Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults, and is characterized by accumulation of immature white blood cells with aberrant proliferation and differentiation blockade. One type of AML is Acute Promyelocytic Leukemia (APL), distinguished by the expression of promyelocytic leukemia (PML)-retinoic acid receptor (RARa) chimeric protein that acts as an antagonist of wild-type RARa. Treatment of APL patients with retinoic acid (RA) promotes at least partial transcriptional de-repression, but unfortunately provides transient clinical remission. Interestingly, we observed that APL-NB4 cell treatment with RA and glucocorticoids markedly enhances cell differentiation (Dif) and potentiates expression of RARa- target genes. Thus, we hypothesize that glucocorticoid receptor (GR) localization and target gene regulation in undifferentiated (Undif) cells somehow determine its subsequent interaction and functional effects along the myeloid differentiation program. Therefore, in our aim to elucidate GR relevance in Undif and Dif cells, we report here that a different nuclear GR distribution is observed in western blots depending on the leukemic context (AML or APL) of cells grown either in full (F) or steroid-deprived (CS) serum-containing medium for 24h. Moreover, by RT-qPCR assays we quantified TTP (Undif-F: 0.33 ± 0.20, Undif-CS: 0.39 ± 0.17, Dif-F: 1.04 ± 0.29, Dif-CS: 0.82 ± 0.10) and DUSP-1 mRNA levels (Undif-F: 0.96 ± 0.32, Undif-CS: 0.63 ± 0.14, Dif-F: 0.57 ± 0.10, Dif-CS: 0.90 ± 0.36), resulting both in induced expression levels in Dif-cells, regardless of serum conditions or in CS-serum, respectively. Furthermore, co-IP experiments reveal a novel GR-RARa complex in Undif-NB4 nuclei, which becomes enhanced in Dif-cells. Collectively these data lead us to suggest that depending on the differentiation context, steroids may present opposing regulatory effects. Further characterization of this molecular context could aid to identify attractive targets for therapeutic strategies in myeloid leukemia.

0677 - TRANSCRIPTIONAL REGULATION IN WHOLE ORGAN MAMMARY GLAND CULTURE MEDIATED BY THE LIVER X RECEPTOR

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Abstract/Resumen: Liver X Receptors (LXRs) belong to the nuclear receptors superfamily of ligand activated transcription factors, being the oxysterols their endogenous ligands. They play a key role in the regulation of the cholesterol homeostasis, induce the expression on genes related to the de novo synthesis of triacylglycerides, and repress pro-inflammatory factors effects. During lactation, the mammary gland is endowed with an enormous capacity to synthesize and secrete lipid in the form of triglycerides and cholesterol esters. In previous studies, we found an increase in milk-cholesterol mediated by LXR activation in vivo. According to this founding, we aimed to study direct influence of LXR activation in the mammary epithelium. Mammary gland explants from C57BL/6JFCEN pregnant mice (15 days post coitum) were differentiated in Waymouth's MB 752/1 culture medium using a lactogenic hormone mix of insulin, aldosterone, hydrocortisone and prolactin. The culture was