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Abstract/Resumen: Introduction The imbalance between reactive oxygen species and nitric oxide is implicated in the pathogenesis of hypertension. Several studies have provided evidence of the role of an impaired glutation (GSH) system in the development of hypertension. Furthermore, N-acetylcysteine (NAC) improves NO bioavailability reducing blood pressure in adult spontaneously hypertensive rats (SHR). Nebivolol is a third-generation beta-blocker that combines beta-adrenergic blocking activity with a vasodilating effect mediated by the endothelial nitric oxide (eNOS) pathway. In the current study, we aimed to examine the effect of chronic oral treatment with the combination of nebivolol and NAC on hemodynamic and histological parameters in normotensive and SHR rats. Four weeks-old female SHR, and control normotensive male Wistar Kyoto rats (WKY) were randomly assigned into 3 groups (n= 10/group): Group 1, WKY without treatment; Group 2, SHR without treatment; and Group 3 (SHR + NAC), which received 0.6 % NAC in drinking water. Two months later rats were randomly assigned into 5 groups: Group 1, WKY without treatment; Group 2, SHR without treatment; Group 3, SHR with nebivolol (15 mg/kg/day); Group 4, (SHR+NAC) which received 0.6 % NAC in drinking water, and Group 5, (SHR+NAC+NEBI), which received NAC plus NEBI. Systolic blood pressure (SBP) was measured in conscious rats by indirect tail-cuff. Furthermore, we measured the mean arterial pressure (MAP) in freely moving rats after carotid cannulation. All rats were sacrificed at the age of 16 weeks. Target organ damage at the left ventricle was evaluated by histological analysis after Sirius red staining. The SBP measured by tail-cuff was significantly reduced in group 5 (SHR+NAC+NEBI) (mmHg; SHR: 181 ± 15 vs. SHR+NAC+NEBI: 155 ± 6, $p<0.05$), although the MAP was significantly reduced by NEBI alone or in combination with NAC (mmHg; SHR+NEBI: 166 ± 7, SHR+NAC+NEBI: 175 ± 14 vs. SHR: 201 ± 10, $p<0.05$). On the other hand, the histological analysis of left ventricle shows a significant reduction on fibrosis interstitial with all the treatments (FCI%, SHR+ NEBI: 0.54 ± 0.21, SHR+NEBI+NAC: 0.84 ± 0.13, NAC: 0.49 ± 0.16 vs. SHR: 1.65 ± 0.40, $p<0.05$). The increased of the size of cardiomyocytes (μm^2, SHR: 725 ± 96, WKY: 449 ± 93, $p<0.05$) was not prevented by any treatment (μm^2, SHR+NEBI: 693 ± 154, SHR+NAC: 707 ± 107, SHR+NEBI+NAC: 575 ± 86) The combination of nebivolol plus NAC was able to prevent the hemodynamic alterations in this model, and markers of organ target damage such as left ventricle fibrosis in SHR rats. Despite nebivolol alone does not modify peripheral SBP in SHR rats, it was able to partially prevent the increase of MAP and the fibrosis on the left ventricle.

Biología celular y molecular de procesos fisiológicos y patológicos / Biology IV

Chairs: Graciela Calabrese | Evangelina Capobianco

0411 - ANALYSIS OF MRP4/ABCC4-INDUCED EPIGENETIC SIGNATURE IN PANCREATIC CANCER

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ININFA

Abstract/Resumen: Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive cancer with a dismal prognosis. Histone deacetylases (HDACs) and demethylases (KDMs), as well as DNA methylases (DNMTs) and demethylases (TETs), are epigenetic modulators whose activity is frequently deregulated in various cancers including PDAC. In particular, HDAC1 and HDAC2 have been shown to play an important role in the control of proliferation, apoptosis, differentiation, migration, and angiogenesis of PDAC cells. The multidrug resistance-associated protein 4 MRP4/ABCC4 is a xenobiotic transporter involved in the regulation of cAMP signaling by extrusion to the extracellular compartment. MRP4 was found highly expressed in PDAC, and its expression correlates with increased proliferation and poor prognosis. MRP4 overexpression in the PDAC cell line BxPC-3 increased proliferation, and cell inoculation in NGS mice produced xenografts with increased weight and poor differentiation compared to mock tumors. Therefore, we aimed to analyze how MRP4 overexpression collaborates in PDAC malignant epigenetic and transcriptional signature that enables tumor progression. We analyzed the expression of several epigenetic modulators in MRP4-overexpressing BxPC-3 tumors (MRP4+), compared to wild type tumors (WT) and tumors transfected with an empty vector (mock). We found increased HDAC1 and HDAC2 mRNA and protein levels, and concomitantly decreased acetylation of H3K9ac, in MRP4+ compared to WT/mock ($p<0.05$). MRP4+ tumors also showed increased mRNA expression of key enzymes involved in epigenetic control of cancer progression: Sirt1 and Kdm1a (LSD1), involved in histone deacetylation and demethylation, and Dnmt1 and Tet1, linked to aberrant methylation/demethylation patterns in DNA. These findings suggest that, in pancreatic cancer, MRP4 contributes to the establishment of an aberrant epigenetic signature and altered transcriptional program which may drive cells towards a proliferative and undifferentiated phenotype.

0520 - RETINOID X RECEPTOR´S ACTIVATION MODULATES A CROSSTALK BETWEEN NRF2 AND NFKB PATHWAY IN RETINAL PIGMENT EPITHELIUM CELLS UPON H_2O_2 TREATMENT

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Abstract/Resumen: Age-related macular degeneration (AMD) is the main pathology leading to blindness in adults and has no cure or effective treatment. Retinal pigment epithelial (RPE) cells have immunomodulatory properties and their degeneration contributes in AMD development. Oxidative stress is also involved in the pathogenesis of this disease. We have demonstrated that RXR activation with HX630 protects RPE (D407) cells from H_2O_2-induced apoptosis, and prevents NFkB nuclear translocation. Also, our previous results suggested RXR-PPARgamma as the main heterodimer involved. In this work we investigate the RXR-PPARgamma involvement in the mentioned protective effect and its mechanism of action. For that, D407 were treated or not with H2O2, HX630 and/or a PPARgamma specific agonist (Pioglitazone: PG). We analyzed cell viability by MTT assay and DAPI stained; and studied NFkB pathway (which modulates inflammation and apoptosis) and Nrf2 (which activates cytoprotective genes and regulates NFkB pathway) by qRT-PCR, florescence microscopy and Western-blot. PG reproduced the inhibition of NFkB translocation and the protective effect of RXR activation against oxidative damage. PG inhibited the IKBalpha phosphorylation more than HX630, while it promoted IKBalpha synthesis. When HX630 and PG were together, the inhibition of NFkB translocation was higher than the agonists alone, although, there was no synergism in apoptosis prevention. HX630 increases Nrf2 synthesis, PG does not, and both agonists together decrease NrF2 levels suggesting proteosomal degradation. As a whole, our results show that RXR and PPARgamma agonists together potentiate the anti-inflammatory response but not the antiapoptotic effects of each agonist alone on RPE cells upon oxidative stress, and suggest that both agonists are necessary together to alter the crosstalk between NrF2 and NFkB pathway.