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INVESTIGATIONS OF THE ROLE OF HYALURONAN ON THE PATHOLOGY OF PULMONARY ARTERY HYPERTENSION IN RAT MODEL

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Abstract:

Background: Idiopathic pulmonary arterial hypertension (IPAH) is a progressive disease that leads to deterioration in cardiopulmonary function and premature death from right ventricular failure. The pathogenesis of IPAH is poorly understood. The pathobiologic features of the disease are aberrant cell proliferation, inflammation and vascular remodeling. Extracellular matrices (ECMs) serve an important role in cell proliferation and migration. A major component of most ECMs is the glycosaminoglycan hyaluronan (HA). We hypothesize that abnormalities in HA levels, modification, and fragmentation result in major regulatory switches causing abnormal SMC proliferation, inflammation, and vascular remodeling in IPAH. This work was supported by The Scientific and Technological Research Council of Turkey (TUBITAK) 112S464.

Methods: While rats in Group 1 (n=12) were provided to breathe with air (normoxia), rats in Group 2 (n=12) were made PAH by feeding in plexiglass chambers which was filled with %10 O_2 for 3,5 weeks after subcutaneously injection 20 mg/kg Sugen-5416. Pulmonary artery pressure (PAP) was recorded with Powerlab device. Lung tissues obtained from PAH and control rats were inflated and embedded in paraffin blocks. The sections were stained with hematoxylin and eosin (H&E) for morphological examination and stained for HA binding protein. Circulation HA was measured by ELISA and HAS gene expressions were examined by Real Time PCR.

Results: Pulmonary artery pressures in PAH hypoxia SU-5416 rat model was founded higher compared to controls. [Pulmonary artery pressure (PAP) mmHg, mean±SD PAH 19.03 ± 1.77, control 10.58 ± 0.40 p=0.00012]. According to ELISA results, statistically higher amount of HA was determined in hypoxia SU-5416 rat model animals compared to the controls [HA ng/mL, mean±SD PAH 3.8 ± 0.41, control 1.96 ± 0.31 p<0.0015]. The accumulation of HA molecule was detected especially in pulmonary arteries which were obtained from PAH rat models. This intensity was higher in the site where especially thickening and smooth muscle cell proliferation were occurred. The expression of HAS1 and HAS3 protein weren't determined in either control or hypoxia Sugen-5416 PAH rats, however, HAS2 protein expression was founded significantly higher in hypoxia Sugen-5416 rats compared to controls [HAS2 protein expression, mean±SD: PAH 2.0 ± 0.5, control 0.86 ± 0.07 p=0.0493]. These results show that hyaluronan accumulation in PAH rat model lung is caused by higher working of HAS2 enzyme. There were not big differences in Hyal2 mRNA expression between hypoxia Sugen-5416 PAH rat models and its control [Hyal2 mRNA expression, mean±SD: PAH 10.9 ± 0.92, control 8.2 ± 1.32 p=0.115], however, HAS2 mRNA expression was found statistically different in hypoxia Sugen-5416 PAH rat model compared to controls [HAS2 mRNA expression, mean±SD: PAH 82.3 ± 6.29, control 41.3 ± 6.0 p=0.00083].

Conclusion: Our findings suggest that high levels of HA in hypoxia Sugen 5416 PAH rat model might have an important role in the pathobiology of the disease and could serve as a biomarker of cellular proliferation and vascular remodeling.

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