Extended Abstract
Volume 5:6, 2021

Journal of Genetics and DNA Research

Open Access

Inhibition of hyaluronan for the treatment of pulmonary hypertension

Harry Karmouty Quintana

University of Texas Health Science Center, USA

Abstract

Pulmonary hypertension (PH) is a highly lethal and widespread lung disorder that is a common complication in chronic lung diseases such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF). Its presence in these chronic lung diseases is the single most significant predictor of mortality. While increased levels of hyaluronan have been observed in IPF patients, hyaluronan-mediated vascular remodeling and the hyaluronan-mediated mechanisms promoting PH associated with IPF are not fully understood. Using explanted lung tissue from patients with IPF with and without a diagnosis of PH we identified increased levels of hyaluronan. These results were consistent with an experimental model of lung fibrosis and PH and in the hypoxia-surgeon model of PH where elevated hyaluronan levels were observed. In both human-derived material and in our experimental models of disease elevated hyaluronan levels were consistent with increased expression of hyaluronan synthases (HAS). Interestingly, we also report increased levels of hyaluronidases in patients with IPF and IPF with PH. This is significant since high molecular weight hyaluronan is associated with protective functions whereas degradation of hyaluronan to low molecular weight fragments is associated with deleterious effects. We next evaluated the potential of 4-methylumbeliferone (4MU), a hyaluronan synthase inhibitor, as a potential therapy for PH in our experimental models of disease. Remarkably, our data also show that 4MU can inhibit PH in our models either prophylactically or therapeutically. Studies to determine the hyaluronanspecific mechanisms revealed that hyaluronan fragments result in increased PASMC stiffness and proliferation but reduced cell motility in a RhoA dependent manner. Taken together, our results show evidence of a unique mechanism contributing to PH that could be exploited therapeutically.

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide. The development of pulmonary hypertension (PH) in patients with COPD is strongly associated with increased mortality. Chronic inflammation and changes to the lung extracellular matrix (ECM) have been implicated in the pathogenesis of COPD, yet the mechanisms that lead to PH secondary to COPD remain unknown. Our experiments using human lung tissue show increased expression levels of the adenosine A2B receptor (ADORA2B) and a heightened deposition of hyaluronan (HA; a component of the ECM) in remodeled vessels of patients with PH associated with COPD. We also demonstrate that the expression of HA synthase 2 correlates with mean pulmonary arterial pressures in patients with COPD, with and without a secondary diagnosis of PH. Using an animal model of airspace enlargement and PH, we show that the blockade of ADORA2B is able to attenuate the development of a PH phenotype that correlates with reduced levels of HA deposition in the vessels and the down-regulation of genes involved in the synthesis of HA.

This work is partly presented at International Conference on Glycobiology