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Inhibition of hyaluronan for the treatment of pulmonary hypertension

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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 hyaluronan-specific 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.

Biography

Karmouty Quintana has received his Undergraduate degree in Pharmacology from King's College London (UK) in 2003. In 2006, he has received his PhD in Pharmacology and Biophysics from King's College London (UK), where he pioneered the use of Magnetic Resonance Imaging (MRI) as a tool to non-invasively image experimental lung disease. From 2006-2010, he was a Postdoctoral Fellow at McGill University, where he was funded by the Fonds de la Recherche en Santé du Québec (FRSQ). He then joined UTHealth in 2010 as Postdoctoral Fellow. In 2015, he became a Tenure-Track Assistant Professor at UTHealth. His research is funded by the American Heart Association (AHA), the American Lung Association (ALA), Genentech, and the NIH.

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