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Title: Role of mir23a and PGC-1 alpha in pulmonary hypertension

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Body: Background: Human pulmonary arterial hypertension (PAH) is a disease largely restricted to small pulmonary arteries. PAH is characterized by vascular remodelling that leads to an increase in vascular resistance with devastating effects. Recently the role of miRNAs have been associated with hypoxia mechanisms events implicated in the remodelling of small arteries that occurs in HAP. We have analyzed differences in expression profiles of miRNA isolated from HAP diagnosed patients compared to healthy donors. We have also used a cellular model of small vascular endothelial and smooth muscle cells exposed to ET-1 and TGF-beta to analyze the role of mir23a modulating cell events implicated in EnMT and proliferation. Methods:RNAs were isolated form peripheral blood extracted from 16 primary PAH diagnosed patients and 12 healthy donors. Blood peripheral miRNAs were analyzed using Affymetrix microarrays. Endothelial and smooth muscle cells were exposed to ET-1 an TFG for up to 72 hours. Gene expression were measured by RT-PCR. Results: We have observed consistent changes in miRNAs which have been previously associated wit HAP, including miR-17 and miR-92, miR-22and miR-21 and miR-23a (implicated in cardiac damage and in inhibiting the expression of PGC-1alpha). siRNA experiment induced an increase in the expression of PGC-1alpha, while PPAR gamma agonist ciglitazone inhibited the molecular changes induced by endothelin and TGF in both endothelial and smooth muscular cells. Conclusion: Our data supports the implication of miRNAs in the progression of HAP and the involvement of miRNA 23 in the control of PGC-1alpha which may by implicated in mitigate remodeling processes associated with changes in small vasculature.