Telaglenastat (CB-839) Selectively Attenuates Increased Mitochondrial Glutaminolysis in Pulmonary Hypertensive Endothelial Cells

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Pulmonary hypertension (PH) is a pulmonary vascular disease exhibiting a high mean arterial pressure (25mmHg at rest). Cellular hyperproliferation contributes to vascular remodeling, leading to the development of PH. During hyperproliferation, cells rely on glutaminolysis and the tricarboxylic acid (TCA) intermediates for ATP and macromolecules production. Glutaminolysis converts glutamine into the TCA cycle metabolites through the regulation of glutaminase 1 (GLS1) and glutamate dehydrogenase (GLUD) enzymes. Student researcher wanted to identify an inhibitor that specifically targets glutaminase 1 within the glutaminolysis pathway and suppresses the hyper-proliferative growth of endothelial cells in PH. Western blot analysis was used to check the levels of GLS1 protein. Results from the Western blot analysis showed increased levels of GLS1 enzymes in PH when compared to controls. Results from the 13C Glutamine flux data received from assistant researcher revealed separation in metabolite profiles between PH and PH with GLS1 inhibitor (CB-839) and changes in metabolite levels between PH endothelial cells and PH endothelial cells treated with CB-839. The level of glutamine remained unchanged but the level of glutamate was significantly down upon treatment with CB-839. Both TCA cycle and linked glutaminolysis metabolic pathways showed decreased metabolic intermediates upon treatment with CB-839. The decrease in glutaminolysis correlated with significant reduction in endothelial cell proliferation. Overall, this study identified increased expression of glutaminase 1 associated with PH and CB-839 specifically reduced glutamate levels suppressing glutaminolysis and the hyperproliferative PAEC growth.

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