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Angiotensin II limits NO production by upregulating arginase through a p38 MAPK–ATF-2 pathway

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Vascular endothelial dysfunction is a major cause of morbidity and mortality in patients with cardiovascular diseases such as hypertension, atherosclerosis and diabetes. Nitric oxide (NO) produced by endothelial nitric oxide synthase (NOS) is needed for normal vascular function. In conditions of vascular dysfunction, elevated levels of arginase can compete with NOS for available L-arginine thus reducing vascular NO production. Elevated angiotensin II (Ang II) is a key participant of endothelial dysfunction in many cardiovascular diseases and has been linked to elevated arginase activity. Our studies have explored the signaling pathway leading to increased arginase expression/activity in responses to Ang II in bovine aortic endothelial cells (BAEC). Treatment of BAEC with Ang II caused an increase in arginase activity. This was accompanied by a decrease in NO production. Our studies indicate involvement of the RhoA/ROCK-p38 mitogen activated protein kinase (MAPK) in Ang II-induced arginase upregulation and reduced NO production, as inhibitors of ROCK or p38 MAPK prevented the Ang II-induced increase in arginase activity. Additionally, treatment of BAEC with Ang II causes phosphorylation of activating transcription factor-2 (ATF-2) and enhancement of the binding of ATF-2 to arginase promoter through an AP-1 site as evident from EMSA experiments. Transfection of BAEC with ATF-2 siRNA prevents Ang II-induced increases in arginase activity/expression and maintains NO production. These results indicate that ATF-2 is necessary for enhanced expression of arginase by Ang II. Collectively, our results indicate that Ang II increases endothelial arginase activity/expression through a RhoA/ROCK-p38 MAPK-ATF-2 pathway leading to reduced NO production and endothelial dysfunction. Targeting these signaling steps might be therapeutic points for preventing vascular endothelial dysfunction associated with elevated arginase levels.

Biography

Alia Shatanawi has completed her PhD in Pharmacology with distinction from The Medical College of Georgia at Georgia Regents University in the United States in 2011. After finishing her PhD, she accepted an Assistant Professor position at the Faculty of Medicine in The University of Jordan, Amman, Jordan. She is a 2014 fellow for the UNESCO L'oreal For Women in Science international program. She also holds a degree in dental surgery from The University of Jordan. She has published many papers and has received numerous awards and recognitions at both the regional and international levels.

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