Hypoxia Effects on MKP-1 Production

Hypertensive disease responses include vascular remodeling through the processes of atherosclerosis and angiogenesis, yet the complexity of the pathway of activation has not been fully elucidated. Vascular remodeling is linked to Angiotensin II and ERK1/2 signal transduction, which leads to activation of cyclic AMP response element binding protein (CREB). Our laboratory has shown that CREB knockout prevents Angiotensin II induction of mitogen activated protein kinase phosphatase 1 (MKP-1) expression. In addition several genes that are upregulated during hypertension, including MKP-1, were shown to have overlapping HRE/CRE promotor regions. Because hypoxia inducible factor-1α (HIF-1α) binds to HRE regions, we tested the hypothesis that Angiotensin II signaling to MKP-1 is affected by hypoxia through the activation of HIF-1α. Cultured vascular smooth muscle cells were transfected with siHIF to prevent HIF-1α expression and hypoxia was induced via cobalt chloride addition. Taqman quantitative PCR was used to amplify the mRNA levels and Western blot was used to determine HIF-1α knockdown. Angiotensin II induced MKP-1 mRNA levels, but this signal was not affected by hypoxia or by knockdown of HIF-1α. It was shown that the HIF-1α protein levels were reduced slightly by the siHIF, but this reduction was not significant enough to consider it a full knockout. MKP-1 results from Western blotting also showed an insignificant effect on expression. Although the methods of HIF-1α knockout and induction of hypoxia were not sufficient to conclude that they affect MKP-1 expression, future experiments using other methods to produce hypoxia and HIF-1 knockdown will be pursued to examine the role of hypoxia in regulating vascular remodeling and hypertensive disease.