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Regulation of MAP Kinase Phosphatase Activity by Reactive Oxygen Species in the Angiotensin II Signal and Tumor Necrosis Factor

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Summary

MAP kinases including ERK, p38 and JNK, play important role in angiotensin II signaling. Angiotensin II induces tumor necrosis factor (TNFα) expression through activation of nuclear factor-kappa B (NF-κB), and both Angiotensin II and TNFα activate several types of NADPH oxidase (NOX) and generate reactive oxygen species (ROS) including O_2^-, H_2O_2, and the hydroxyl radical ($OH^\cdot$) in endothelial cell, vascular smooth muscle cells, neutrophils, and macrophages. O_2^- and H_2O_2 are readily converted into the hydroxyl radical ($OH^\cdot$) by Fenton reaction in the presence of Fe. Recent studies have revealed that ROS mediates angiotensin II and TNF signaling and are involved in vascular disorders. However, it was unclear how ROS activate MAP kinases in angiotensin II and TNF signaling pathways. Here we found that $OH^\cdot$ scavenger thiourea effectively suppresses H_2O_2-induced MAP kinase activation indicating an essential role of $OH^\cdot$ in oxidative stress-induced MAP kinase activation. Accumulation of ROS inactivates MAP kinase phosphatases (MKPs) by oxidation of their catalytic cysteine, which in turn leads to activation of MAP kinases. TNFα also stimulates MAP kinases by inactivation of MKPs through generated ROS and promotes cell death in NF-κB-deficient cells. Furthermore, we found that ROS induce IκBα degradation by association with βTrCP in a specific manner resulting in NF-κB activation. These results suggest that generation of ROS by angiotensin II and TNFα is involved in a number of vascular disorders, including hypertension and atherosclerosis, through activation of MAP kinases and NF-κB.