Mechanisms of Cytoskeletal Dysregulation in the Kidney Proximal Tubule During ATP Depletion and Ischemia

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Abstract:

Knowledge of the molecular and cellular mechanisms of ischemic injury is necessary for understanding acute kidney injury and devising optimal treatment regimens. The cortical actin cytoskeleton in the proximal tubule epithelial cells of the kidney nephron, playing an important role in both the establishment and maintenance of cell polarity, is drastically disrupted by the onset of ischemia. We found that in LLC-PK cells (a porcine kidney proximal tubule epithelial cell line), cortactin, an important regulator of actin assembly and organization, translocated from the cell cortex to the cytoplasmic regions upon ischemia/ATP-depletion. Meanwhile both the tyrosine phosphorylation level of cortactin and cortactin’ s interaction with either F-actin or the actin nucleator Arp2/3 complex were down-regulated upon ischemia/ATP-depletion or inhibition of Src kinase activity. These results suggest that tyrosine phosphorylation plays an important role in regulating cortactin’ s cellular function and localization in the scenario of kidney ischemia. The Rho GTPase signaling pathways is also

a critical mediator of the effects of ATP depletion and ischemia on the actin cytoskeleton, but the mechanism by which ATP depletion leads to altered RhoA and Rac1 activity is unknown. We propose that ischemia and ATP depletion result in activation of AMP-activated protein kinase (AMPK) and that this affects Rho GTPase activity and cytoskeletal organization (possibly via TSC1/2 complex and/or mTOR complex). We found that AMPK was rapidly activated (≤5 minutes) by ATP depletion in S3 epithelial cells derived from the proximal tubule in mouse kidney, and there was a corresponding decrease in RhoA and Rac1 activity. During graded ATP-depletion, we found intermediate levels of AMPK activity at the intermediate ATP levels, and that the activity of RhoA and Rac1 activity correlated inversely with the activity of AMPK. Activation of AMPK using two different drugs suppressed RhoA activity, and also led to morphological changes of stress fibers. In addition, the inhibition of AMPK activation partially rescued the disruption of stress fibers caused by ATP-depletion. This evidence supports our hypothesis that the activation of AMPK is upstream of the signaling pathways that eventually lead to RhoA inactivation and cytoskeletal dysregulation during ATP-depletion.

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