No. 1732

# Analysis of a Novel Mechanism of p38 MAPK Activation by High Salt, Which Drives Autoimmune Disease

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Summary

It was reported that excessive dietary salt intake might increase the risk of developing autoimmune diseases. One of crucial factors was shown to be the p38 MAP kinase (MAPK) that is activated by high osmolarity upon high salt conditions. p38 is a stress responsive MAPK, which is activated by various kinds of environmental stresses for adaptation and inflammation. However, the mechanism of sensing high osmolarity in the p38 MAPK pathway remains largely elusive.

To get an insight into the osmosensing mechanism in the p38 MAPK pathway, we, first, investigated the osmosensing mechanisms in the yeast osmoregulatory Hog1 MAPK pathway. Hog1 is a prototype of p38, and both MAPKs have conserved structures and functions. In this study, we found that activation of Hog1 by high osmolarity requires, in addition to the previously identified transmembrane osmosensors (Sho1/Opy2/Hkr1, Sho1/Opy2/Msb2 and Sln1), a fourth, cytoplasmic osmosensor, which is actually Hog1 itself. The properties of a constitutively-active Hog1 mutant suggest a two-step activation mechanism, in which a conformational change of Hog1 by osmostress is necessary to allow it to be activated/phosphorylated by Pbs2 that has been activated separately by upstream osmosensors. Interestingly, the introduction of equivalent mutations of a constitutively-active Hog1 mutant conferred higher kinase activity to the mammalian p38 MAPK, suggesting a possibility that p38 activation by high osmolarity also requires both osmotic stimulation of the upstream sensors and osmotic priming of p38 itself.