

P015 Involvement of Rho in the activation of p38 α in cerebellar granular neurons

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Rho GTPases control a variety of cell functions through the regulation of multiple signal transduction pathways. Rho is known to selectively activate p38 β but not p38 α in cell lines and is involved in inhibition of neurite regeneration and release of amyloidogenic A β_{42} peptide. Glutamate, the major excitatory neurotransmitter of the brain, is also responsible for excitotoxic neuronal cell death in ischaemia, and may contribute to other neurodegenerative conditions. Here we show that Rho is activated by glutamate addition to cerebellar granular neurons, our model of excitotoxicity, and required for rapid activation of p38 α and excitotoxic cell death. We demonstrated rapid activation of neuronal Rho following glutamate treatment, by pull-down assay and by the fluorescence-resonance energy transfer (FRET) probe of Rho activation, Raichu-RBD. Co-transfection experiments with C3 exoenzyme, which ADP-ribosylates Rho and prevents it from interacting with effectors, protect the neurons from death, and prevent activation of p38 α subsequent to glutamate treatment. The ability of RhoA to activate p38 α was unexpected from the literature, and we found it was specific to primary neuronal cultures. Taken together our data reveal Rho as a novel and essential component of the excitotoxic cell death pathway.