

Dynamics of Extracellular Signal-Regulated Kinase (ERK) Activation in Developing Cerebellar Granule Cells (CGC): A Systems Biology-Oriented Study

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ERK is a regulator of neuronal survival and growth and its activation is susceptible to perturbation by environmental chemicals. The objective of this study was to 1) characterize the dynamics of ERK activation in response to BDNF and NMDA; 2) use computational models to promote understanding of the signaling network underlying ERK activation. Dual-phosphorylated ERK was measured in rat CGC on DIV 7. Cells were treated with either a 5-min pulse or continuous BDNF or NMDA for up to 2 hrs. For both BDNF (50 ng/ml) and NMDA (50 μ M), ERK activation was biphasic. A fast rise in phosphorylated ERK, peaking at 10-30 min, was followed by a slow increase to 120 min. In contrast to the 5-min treatment, continuous stimulation caused a slight dip in ERK activity between the fast and slow phases. To help interpret these results, we constructed a computational model of the signaling cascade from TRK or NMDAR activation at the cell membrane to cytosolic ERK activation. The biphasic activation can be explained by sequential activation of two positive feedback loops CGC. The first feedback has a fast dynamic and possibly involves the core MAPK cascade (Bhalla et al, Science 2004). This feedback accounts for the initial fast rise in phosphorylated ERK may ensure subsequent activation of the second feedback. The second feedback may be transcriptionally regulated as it starts later time and causes slower up-regulation of ERK. Interestingly, the slow rising phase of ERK activation in CGC was not seen in the NIH 3T3 fibroblasts studied by Bhalla et al (ibid). In the fibroblasts, the rapid initial activation of ERK is followed by a gradual decline in activated ERK mediated by transcriptional induction of ERK phosphatase. Thus, NIH 3T3 cells and CGC appear to differ in the transcriptionally mediated regulation of activated ERK.

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Notes for Sandy:

Mundy and Conolly are SOT members

Zhang is not an SOT member

Conolly will be the presenting author