The scaffold protein JSAP1 regulates proliferation of cerebellar granule cell precursors by modulation JNK signaling

T. Sato, T. Torashima, K. Sugihara, H. Hirai, M. Asano and K. Yoshioka

Cerebellar granule cell precursors (GCPs) proliferate in the outer part of the external granular layer (EGL). They begin their differentiation by exiting the cell cycle and migrating into the inner part of the EGL. Scaffold proteins for mitogen-activated protein kinase (MAPK) pathway are though to function in the spatial and temporal regulation of these pathways by organizing the MAPK signaling components into functional modules. Our group previously identified JNK/stress-activated protein kinase-associated protein 1 (JSAP1, also known as JNK-interacting protein 3 (JIP3)) as a scaffold protein for mammalian JNK MAPK pathway. Here we report that JSAP1, a scaffold protein for JNK signaling pathway, is expressed predominantly in the post-mitotic GCPs of the inner EGL. JSAP1 knockdown or treatment with a JNK inhibitor enhances proliferation of cultured GCPs, but the overexpression of wild-type JSAP1 leads to increased proportions of $p27^{Kip1}$- and NeuN-positive cells, even with saturating concentration of Sonic hedgehog (Shh), a potent GCP mitogen. However, these differentiation-promoting effects on GCPs are attenuated significantly in cells overexpressing a mutant JSAP1 that lacks the JNK-binding domain. Together, these data suggest that JSAP1 antagonizes the mitogenic effect of Shh on GCPs and promotes their exit from the cell cycle and differentiation, by modulating JNK activity.

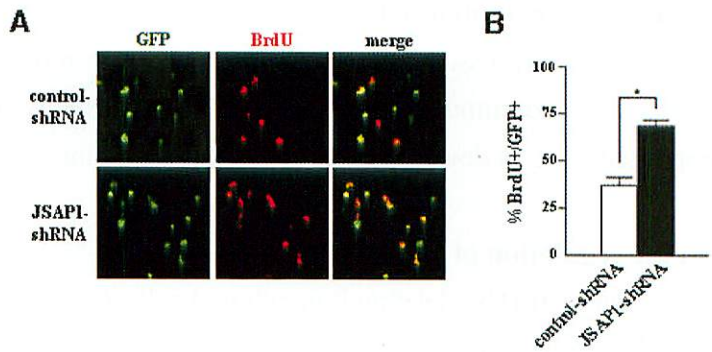

Figure Knockdown of JSAP1 expression enhances the proliferation of cultured GCPs. (A) Double Immunofluorescence of P4 cultured GCPs infected with lentiviruses expressing GFP plus either control-shRNA or JSAP1-shRNA, 72 h after infection. They were stained with antibodies to GFP (green) and BrdU (red). (B) The percentage GFP-positive cells that were BrdU-positive in cultures infected with the control lentivirus or lentivirus containing the JSAP1-shRNA (mean + SEM from 3 experiments, $*p < 0.005$, Student's *t*-test).

Reference:

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