

## **A Role of R-Ras in Repulsive Response of Axon Guidance Factors, Semaphorins**

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Axon guidance represents a key stage in the formation of neuronal network. Axons are guided by a variety of guidance factors, such as semaphorins, ephrins and netrin. Plexins function as receptors for the repulsive axonal guidance molecules semaphorins. We have revealed that the semaphorin 4D (Sema4D) receptor Plexin-B1 directly stimulates the intrinsic GTPase activity of R-Ras, which has been shown to promote neurite outgrowth by activating integrins, in response to Sema4D. The down regulation of R-Ras activity by the Plexin-B1 is essential for the Sema4D-induced growth cone collapse in hippocampal neurons. In addition, the downregulation of R-Ras activity is also required for the Sema3A-induced growth cone collapse. Thus, Plexins mediate semaphorin-induced repulsive signaling by acting as a GAP for R-Ras. We here characterized the downstream signaling of Plexin-B1-mediated R-Ras GAP activity. Sema4D suppressed R-Ras activity in hippocampal neurons and dephosphorylated Akt and GSK-3 $\beta$  and phosphorylated CRMP-2, a microtubule polymerization stimulator, through its inhibition of R-Ras activity. Therefore, Plexin-B1 inactivates PI-3K and Akt, and activates GSK-3 $\beta$  through R-Ras GAP activity, inducing growth cone collapse.