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Generation and analysis of Plexin-B1 and Plexin-B2 mutants in mice

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The work of the present project can be summarized in three main points. Generation and analysis of mice constitutively lacking the *plxnb1* gene. Here, we have shown that a loss of Plexin-B1 expression in mice does not lead to obvious defects and in particular does not significantly impact upon the development of the peripheral and central nervous system.

Generation and analysis of mice lacking the *plxnb2* gene. Mice lacking Plexin-B2 expression demonstrated defects in closure of the neural tube and a conspicuous disorganization of the embryonic brain with a penetrance of 88%. Upon analyzing mutant mice which bypassed neural tube defects, we observed a key requirement for Plexin-B2 in proliferation and migration of granule cell precursors (GCPs) in the developing dentate gyrus, olfactory bulb and cerebellum. The retarded migration of granule cell precursors in the developing dentate gyrus, olfactory bulb and cerebellum has also been observed in the mutants with normal neural tube closure, which excluded the possibility that the migration abnormality of GCPs in mutants with neural tube closure defects is secondary to defects in neural tube development. In addition, enlarged ventricle and ventricular ectopias were found in Plexin-B2 mutants.

We identified semaphorin 4C as a putative high-affinity ligand for Plexin-B2 in binding and functional assays. Semaphorin 4C stimulated activation of ErbB-2 and RhoA via Plexin-B2 and enhanced proliferation and migration of granule cell precursors. Semaphorin 4C-induced proliferation of neuroblasts from ventricular zone was abrogated in mice lacking Plexin-B2. Furthermore, Sema4c mRNA expression is detectable either in those cell populations which express Plexin-B2 mRNA or in their close proximity or target zones in the developing olfactory bulb, dentate gyrus and cerebellum which suggests that Sema4C-Plexin-B2 may function as a potential ligand-receptor pair in these regions. Importantly, functional assays revealed that proliferative effects of Sema4C are abrogated in mice lacking Plexin-B2, consistent with phenotypic defects in *plxnb2*$^{-/-}$ mice. Taken together, our expression analysis, the high affinity and specific nature of Sema4C-Plexin-B2 binding and functional experiments demonstrate that Sema4C-Plexin-B2 can function as a true ligand-receptor pair in vivo.