DEVELOPMENT

New rules of attraction

The interaction between CXC-chemokine ligand 12 (CXCL12) and CXC-chemokine receptor 4 (CXCR4) plays a key part in cell migration during CNS development. More recently, CXCR7 has also been identified as a receptor for CXCL12, but the physiological significance of this finding was unknown. Two papers in *Neuron* now show a role for CXCR7 in the developing CNS that is distinct from, but interacts with, the role of CXCR4.

Both studies focused on cortical interneurons in the mouse embryo, which migrate according to gradients of chemotactic signals such as CXCL12. Wang *et al.* showed that knockout of either CXCR4 or CXCR7 led to abnormal interneuron migration and polarization at embryonic day 15.5. Confocal live imaging revealed differential effects in the two knockout mouse strains at the cellular level, highlighting distinct roles for these CXCL12 receptors.

Next, Wang *et al.* used *in utero* electroporation to ectopically express CXCL12 in embryos. The accumulation of interneurons around the site of electroporation in wild-type embryos was absent in *Cxcr4*$^{-/-}$ and *Cxcr7*$^{-/-}$ embryos. Furthermore, pharmacological inhibition of either receptor blocked the chemotactic response of interneurons to CXCL12 *in vitro*. Therefore, both receptors have important, non-redundant roles in neuronal migration.

Previous work showed that CXCR4 signals through $G\alpha_{i/o}$ G proteins and suggested, by contrast, either that CXCR7 is a non-signalling receptor or that it activates the mitogen-activated protein kinase (MAPK) cascade through β-arrestin. Accordingly, inhibition of $G\alpha_{i/o}$ with pertussis toxin produced embryos that phenocopied *Cxcr4*$^{-/-}$ mutants. Furthermore, the increase in MAPK signalling induced by application of CXCL12 was unaffected in *Cxcr4*$^{-/-}$ cells but absent in *Cxcr7*$^{-/-}$ cells in culture. Thus, activation of CXCR7, but not CXCR4, induces MAPK signalling.

Building on these findings, Sánchez-Alcañiz *et al.* delineated a novel cooperation between CXCR4 and CXCR7 through CXCL12. They reported the surprising finding that CXCR4 protein levels are lower in the cortex of *Cxcr7*$^{-/-}$ mutants than wild-type controls. Given the known response of CXCR4 degradation following persistent stimulation, the authors proposed that the absence of CXCR7 to bind excess CXCL12 could lead to increased CXCL12–CXCR4 signalling and CXCR4 internalization. In support of this 'scavenger role' for CXCR7, the concentration of CXCL12 was higher in cortical cultures from *Cxcr7*$^{-/-}$ embryos than wild-type embryos. Moreover, antibody labelling revealed that CXCR7 is predominantly localized to subcellular compartments and recycles between these compartments and the plasma membrane.

Together, these studies show that both CXCR4 and CXCR7 are essential for neuronal migration, and exert their effects through distinct pathways that interact at the level of their shared ligand.

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ORIGINAL RESEARCH PAPERS Wang, X. *et al.* CXCR4 and CXCR7 have distinct functions in regulating interneuron migration. *Neuron* **69**, 61–67 (2011) | Sánchez-Alcañiz, J. A. *et al.* Cxcr7 controls neuronal migration by regulating chemokine responsiveness. *Neuron* **69**, 77–90 (2011)