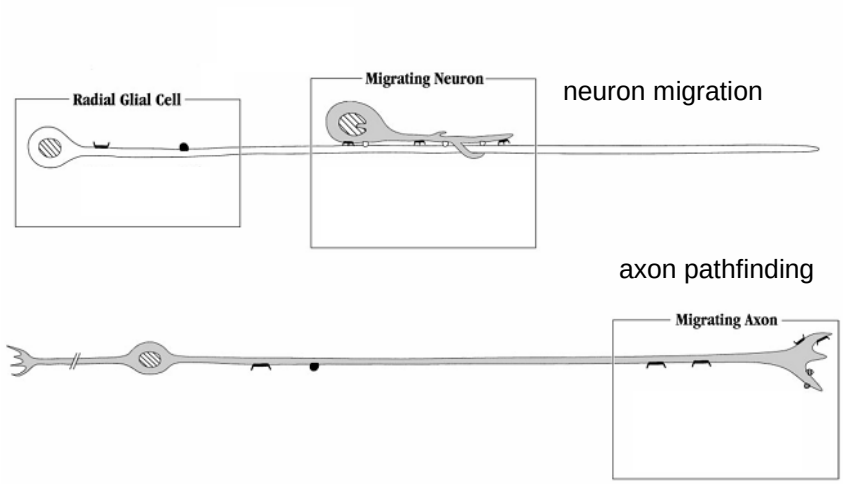
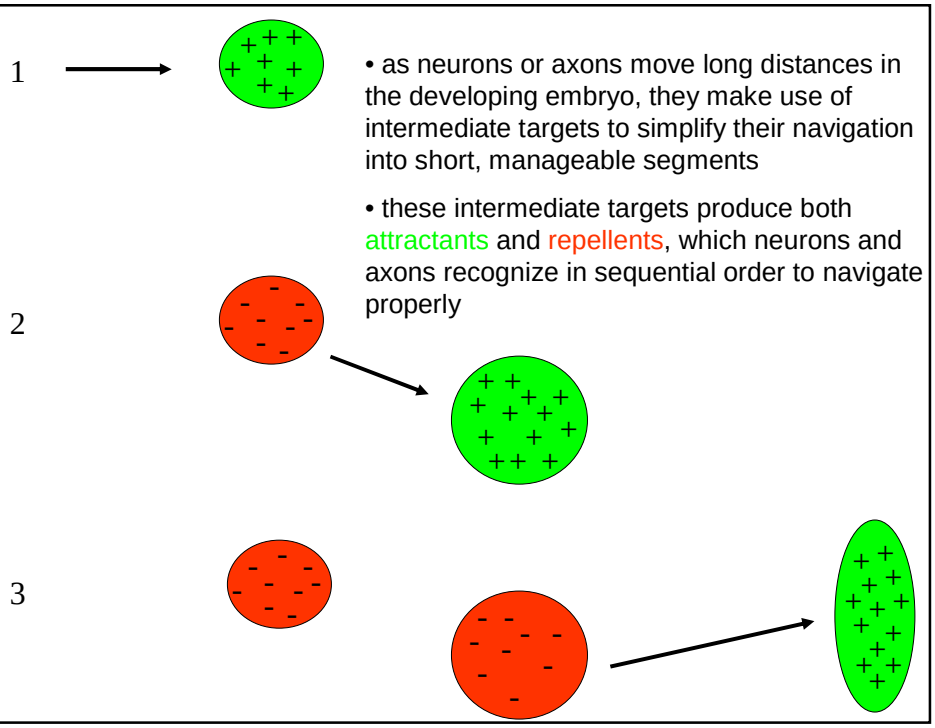
Neuronal migration
&
axon pathfinding

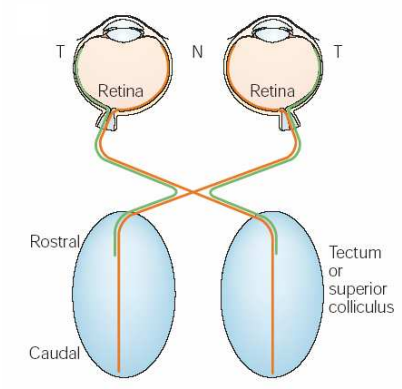
Neuronal migration and axon pathfinding

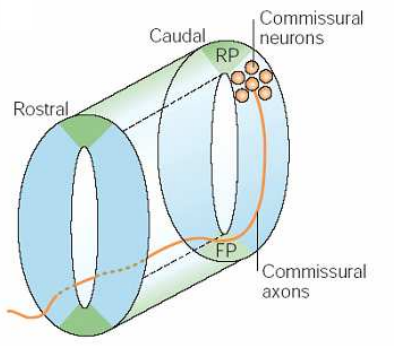
migrating neurons are guided by molecular cues that also guide the **projection of axons**

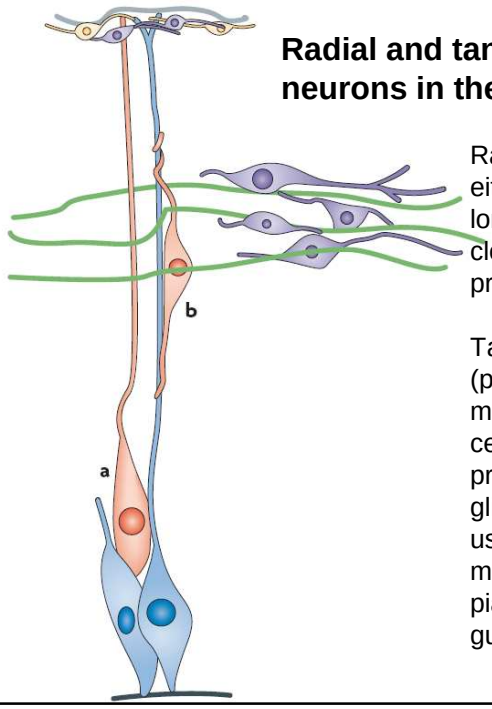




Molecular control of axon pathfinding





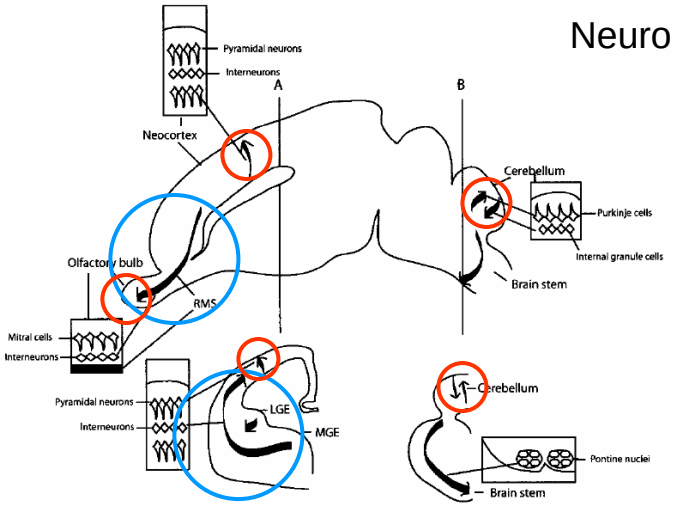


Radial and tangential migration of neurons in the developing cortex.

Radially migrating neurons either use somal translocation with a long leading process (**a**) or migrate in close apposition (**b**) to a radial glial process (blue).

Tangentially migrating neurons (purple) invade the cortex along the marginal zone or through the cerebral wall in a manner that is presumed to be independent of radial glia. These neurons are thought to use corticofugal fibres (green), marginal zone neurons (yellow) or the pial membrane (grey) as migratory guides.

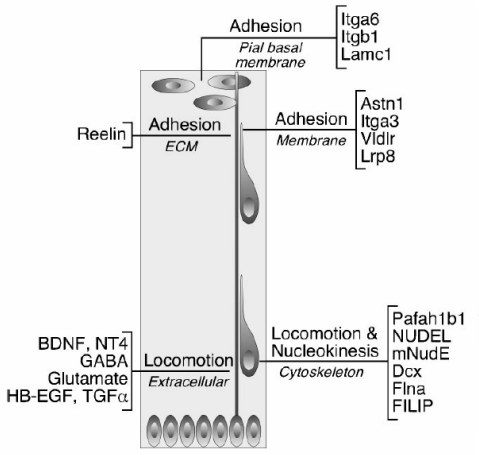
Neuronal migration



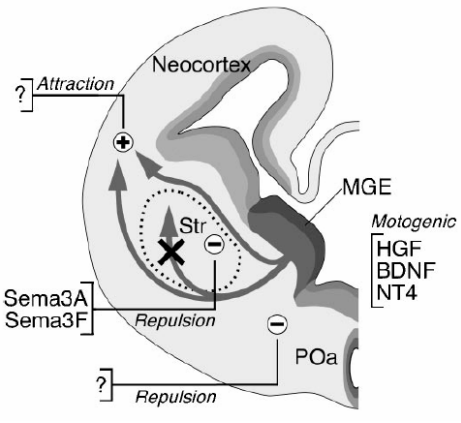
• **radial migration** is involved in the development of pyramidal cells in the cortex and cerebellar granule cells

• **tangential migration** is important for the development of interneurons in the cortex and olfactory bulb, and pontine nuclei of the brain stem

A, B: Coronal sections at the levels of A and B. Abbreviations: RMS, rostral migratory stream; LGE and MGE, lateral and medial ganglionic eminences



Mechanisms regulating **radial** migration in the cerebral cortex. Shown is a schematic representation of radially migrating neurons in the developing cortex, where the ventricular zone is to the bottom and the marginal zone is to the top. Molecules involved in radial migration are indicated in relation to their function (e.g., locomotion) and location (e.g., extracellular).

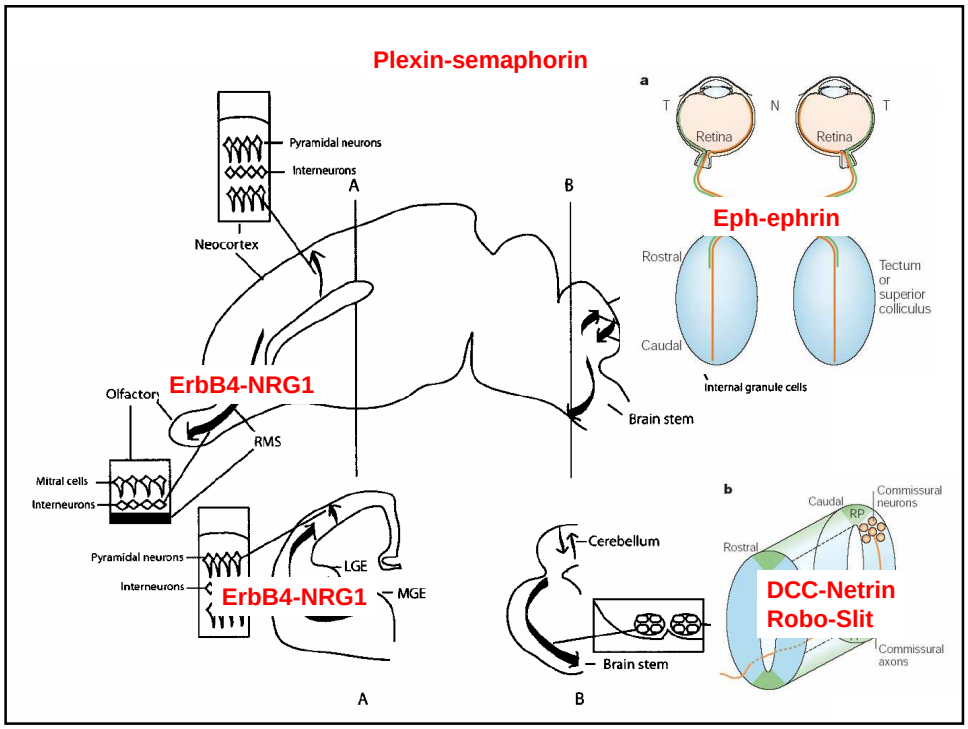


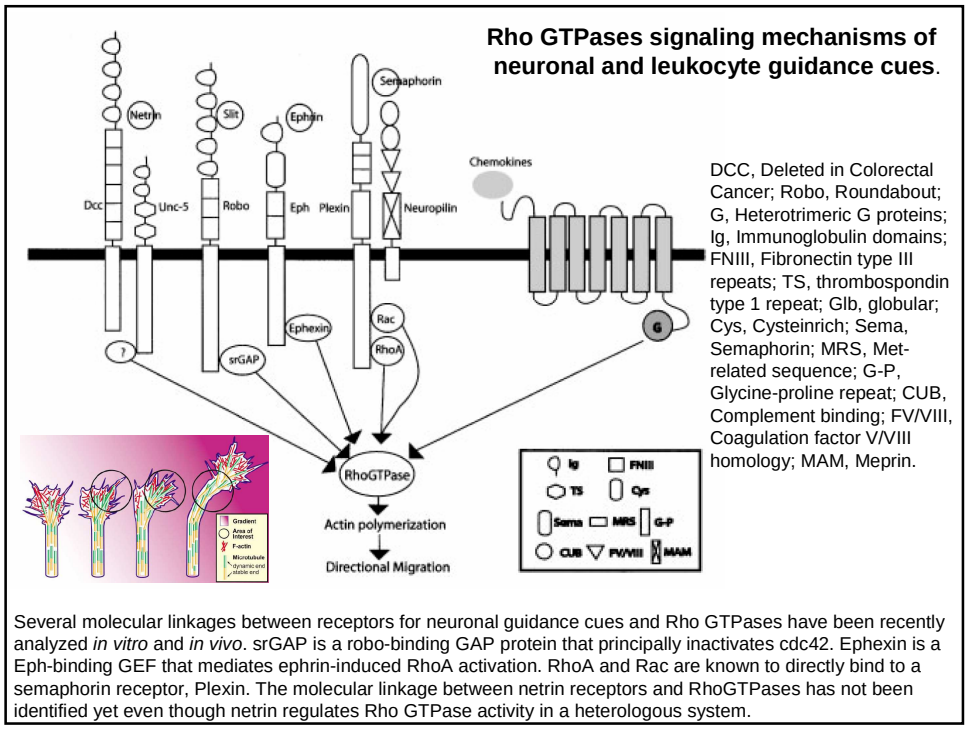
Mechanisms regulating interneuron **tangential** migration from the subpallium to the cerebral cortex. Schematic drawing of a transversal section through the telencephalon in which the midline is to the right and dorsal is to the top. Several motogenic factors promote the migration of neurons from the medial ganglionic eminence (MGE).

Table 1. Directional Guidance cues involved in CNS neuronal migration in vivo and in vitro

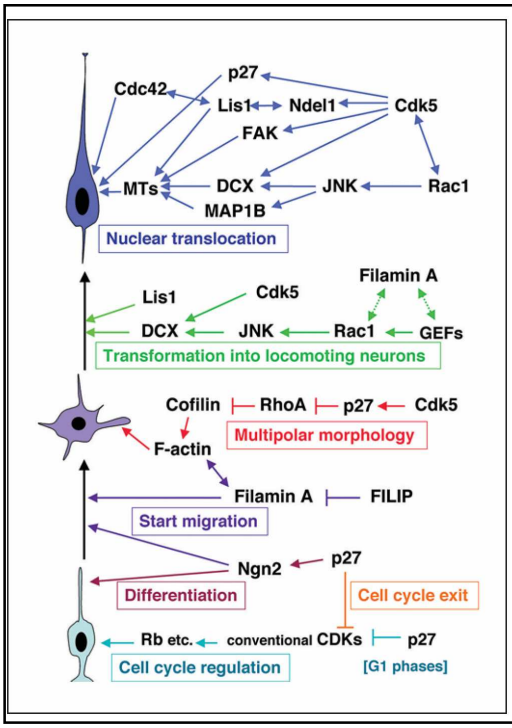
Ligands	Receptors	Defects in CNS neuronal migration in vivo	Neuronal migration in vitro
Slits	Robo	—	1. Slit repels postnatal SVZa cells[37] 2. Slit repels prenatal SVZ cells of GE[43]
Netrins	DCC	1. Abnormal pontine nuclei in DCC and netrin-1 mutants[46]	1. Netrin-1 attracts pontine nuclei[11]
	Unc-5h	2. Abnormal cerebellar development in unc-5h3[64]*	2. Netrin-1 repels postnatal cerebellar granule cells and prenatal SVZ cells[48,49] 3. Anti-DCC antibody blocks directed migration of postnatal SVZa cells[47]
Semaphorins	Neuropilin Plexin	1. Abnormal GABAergic interneurons in the striatum in neuropilin-2 mutants[50]	—
Ephrins	Eph	—	1. Disruption of Eph-B/Ephrin-B system affects the migration of postnatal SVZa cells[51]

*Unc-5h3/RCM mutant mice showed abnormal development of cerebellum. However, it is still unclear that the defect is primarily caused by migration abnormality or other reasons.

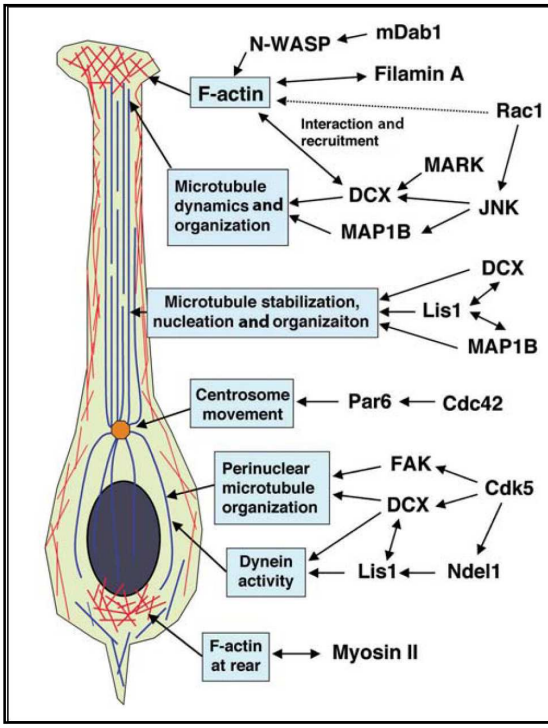




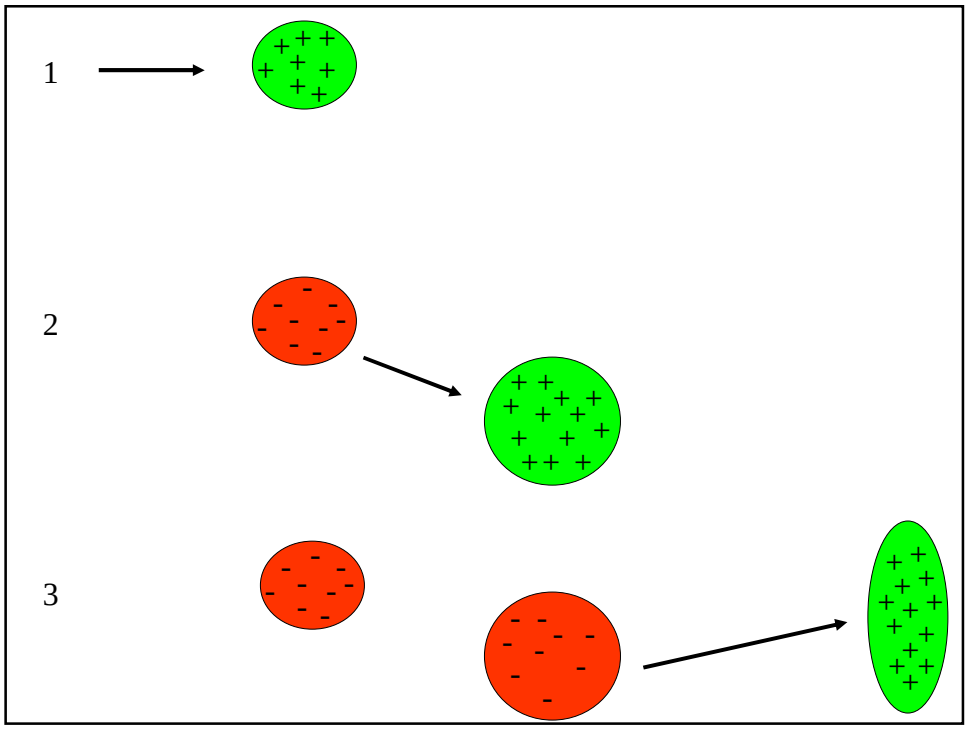
Several molecular linkages between receptors for neuronal guidance cues and Rho GTPases have been recently analyzed *in vitro* and *in vivo*. srGAP is a robo-binding GAP protein that principally inactivates cdc42. Ephexin is a Eph-binding GEF that mediates ephrin-induced RhoA activation. RhoA and Rac are known to directly bind to a semaphorin receptor, Plexin. The molecular linkage between netrin receptors and RhoGTPases has not been identified yet even though netrin regulates Rho GTPase activity in a heterologous system.

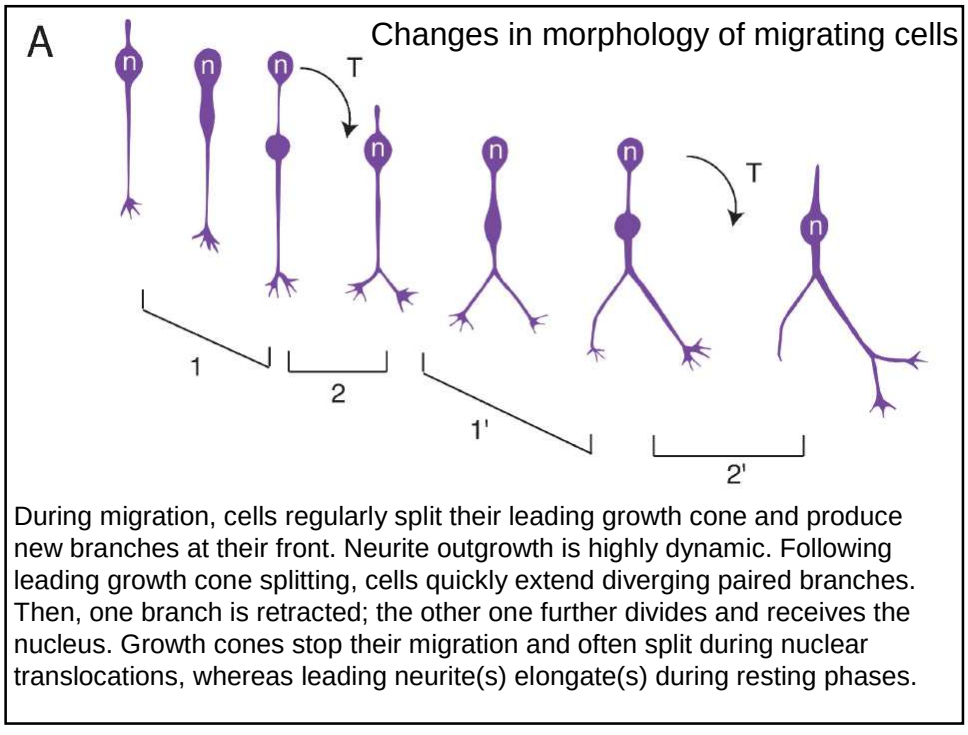


Molecular pathways regulating the morphological changes of migrating neurons.
After the exiting cell cycle, newly generated neurons display multipolar morphology. **p27** is involved in the suppression of conventional cyclin-dependent kinases (**CDKs**), upregulation of Neurogenin2 (**Ngn2**) and activation of an actin binding protein, **cofilin**, to regulate cell cycle exit, neuronal differentiation and migration, respectively. The **Cdk5-p27** pathway regulates multipolar cell morphology, whereas the **Rac1-JNK** pathway participates in leading process formation probably through **DCX**. Cyclin-dependent kinase 5 (**Cdk5**) is also involved in leading process formation and promotes nuclear translocation via phosphorylation of many microtubule (**MT**)-regulatory proteins, such as **FAK**, **Ndel1** and **DCX**.



Subcellular regulatory mechanisms of neuronal migration.
Blue and red lines show microtubules and F-actin, respectively.
Gray circle indicates the nucleus, and orange polygon represents the centrosome (microtubule-organizing center).





During migration, cells regularly split their leading growth cone and produce new branches at their front. Neurite outgrowth is highly dynamic. Following leading growth cone splitting, cells quickly extend diverging paired branches. Then, one branch is retracted; the other one further divides and receives the nucleus. Growth cones stop their migration and often split during nuclear translocations, whereas leading neurite(s) elongate(s) during resting phases.