Receptor tyrosine kinase ErbB4 modulates neuroblast migration and placement in the adult forebrain

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Neural progenitor proliferation, differentiation and migration are continually active in the rostral migratory stream of the adult brain. Here, we show that the receptor tyrosine kinase ErbB4 is expressed prominently by the neuroblasts present in the subventricular zone and the rostral migratory stream. The neuregulins (NRG1–NRG3), which have been identified as ErbB4 ligands, are detected either in the stream or in adjacent regions. Mice deficient in ErbB4 expressed under the control of either the nestin or the Ngfap promoter have altered neuroblast chain organization and migration and deficits in the placement and differentiation of olfactory interneurons. These findings suggest that ErbB4 activation helps to regulate the organization of neural chains that form the rostral migratory stream and influences the differentiation of olfactory interneuronal precursors.
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.
Neuregulin and erbB Receptors Play a Critical Role in Neuronal Migration

- the migration of neuronal precursors along radial glial fibers is a critical step in the formation of the nervous system
- neuregulin–ErbB receptor signalling plays a crucial role in the migration of cerebellar granule cells along radial glial fibers
- granule cells express neuregulin (NRG), and radial glia cells express ErbB4 in the developing cerebellum and in vitro
- when the glial ErbB receptors are blocked, neurons fail to induce radial glia formation, and their migration along radial glial fibers is impaired
- soluble NRG is as effective as neuron–glia contact in the induction of radial glia formation

→ the activation of glial ErbB4 by NRG is an early critical step in the neuronal migration program.

Model for central nervous system neuronal migration along radial glial fibers.

As the neuron migrates, it extends a motile, leading process that wraps around the glial guide. Among cell adhesion receptor systems, astrotactin (Atn) provides neuron-glial ligand. Components of the extracellular matrix may also play a role. However, these likely function in axon extension. The molecular components of the migratory process and the migrating axon, the parallel fiber, are contrasted.
Glial Expression of DN-ErbB4 Blocks Neuronal Migration

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<th>glial cells + freshly dissociated granule cells</th>
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DN-ErbB4+GFP + freshly dissociated granule cells

(A) Most granule cells move significant distances along the control fibers (white arrow), and only a few fail to move (black arrow). (B) At least four granule cells are positioned on this glial fiber, and they exhibit only very slight movements during the period examined (black arrows).

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 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).
• neuregulin receptor ErbB4 is preferentially expressed by interneurons that are migrating tangentially from the ventral to the dorsal rat telencephalon.

• ErbB4-positive migratory streams consisting of cells double-labeled with ErbB4 and Dlx, a marker of tangentially migrating cells, were found to advance along the lower intermediate zone and the marginal zone from the ventrolateral to the dorsomedial cortex at E16–E18.

ErbB4 is co-localized with Dlx in cells of the migratory streams
Schematic summary of the progression of tangential migration of ErbB4-positive interneurons from the ventral to the dorsal telencephalon of rats during development.

ErbB4-positive cells appear in the MGE as early as E13 and then migrate via the LGE into the lateral parts of the cerebral cortex at E15–E16. By E17, ErbB4-positive cells have reached the medial parts of the cortex. They begin to enter the hippocampal primordium at E18. After E20, they migrate deeply into the hippocampal primordium.

CTX, cerebral cortex; HP, hippocampus, MGE, medial ganglionic eminence, LGE, lateral ganglionic eminence.
Complementary expression of *Nrg1* isoforms and *ErbB4* in the developing telencephalon during the period of interneuron migration to the cortex (E 13.5)

* *Nrg1-CRD* is expressed throughout the LGE, from the subventricular zone to the developing striatal mantle

* the developing cortex - the target of the migrating *ErbB4*+ interneurons - specifically expressed the diffusible form of the *Nrg1* gene, *Nrg1-Ig*

* the analysis of adjacent sections revealed that the tangentially migrating *ErbB4*+ cells follow a corridor through the LGE that is *Nrg1-CRD*+ and that lacks *Semaphorin3A/3F* (*Sema3A/3F*) expression
• Semaphorin3A (Sema3A) and Semaphorin3F (Sema3F) were found to be expressed in the striatal mantle where they create an inhibitory territory that migrating cortical interneurons avoid in their way toward the cortex.

• ErbB4-expressing interneurons reach the cortex through a cellular corridor expressing Nrg1-CRD avoiding the striatal mantle due to Sema3A/3F-mediated chemorepulsion.

MGE-Derived Cells Prefer a *Nrg1-CRD*-Expressing Substrate in the Stripe Choice Assay

Slides were coated with alternating stripes of nontransfected COS cells (dark gray dots) and either mock-transfected or Nrg1-CRD-transfected COS cells (red dots). Dissociated E13.5 MGE cells (green dots) were plated on top of the stripe carpets, and their distribution was studied 24 hr later.
NRG1-Ig is a chemoattractant for MGE-derived neurons

Medial ganglionic eminence (MGE) explants from the telencephalon of E13.5 embryos were cultured in Matrigel adjacent to mock-transfected (A) or Nrg1-Ig-transfected (B) COS cell aggregates.

ECTOPIC EXPRESSION OF NRG1-Ig REDIRECTS THE MIGRATION OF MGE-DERIVED CELLS IN SLICE CULTURES

Coronal slice through the telencephalon with cell aggregates formed with control (left) and Nrg1-Ig (right) transfected COS cells. Dil-labeled cells (arrowheads) from both the ipsilateral and contralateral MGE (asterisk) migrate ectopically in a ventrolateral direction toward the COS cell aggregate expressing NRG1-Ig.
different isoforms of neuregulin-1 are expressed in the developing cortex and in the route that migrating interneurons follow toward the cortex, whereas a population of the migrating interneurons express ErbB4, a receptor for neuregulin-1

the different isoforms of neuregulin-1 - type III and type I- act respectively as short- and long- range attractants for migrating interneurons

perturbing ErbB4 function in vitro decreases the number of interneurons MGE that tangentially migrate to the cortex

in vivo, loss of neuregulin-1/ErbB4 signalling causes an alteration in the tangential migration of cortical interneurons and a reduction in the number of GABAergic interneurons in the postnatal cortex

these observations provide evidence that neuregulin-1 and its ErbB4 receptor directly control neuronal migration in the nervous system