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SCIENCE DIRECT

Brain Research Reviews 49 (2005) 253–266

BRAIN RESEARCH REVIEWS

www.elsevier.com/locate/brainresrev

Review

Development of precerebellar nuclei: Instructive factors and intracellular mediators in neuronal migration, survival and axon pathfinding

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Accepted 6 January 2005
Available online 10 March 2005

Abstract

The precerebellar system provides an interesting model to study tangential migrations. All precerebellar neurons (PCN) are generated in the most alar part of the hindbrain in a region called rhombic lip. PCN first emit a leading process and then translocate their nuclei inside it, a mechanism called nucleokinesis. In the past few years, molecular cues that could affect those processes have been investigated, with a special care on: (i) the identification of extrinsic factors directing cell migration and axon elongation as well as neuronal survival during development; (ii) intracellular reorganizations of the cytoskeleton during nucleokinesis in response to chemotropic factors. The signaling cascades, including regulators of actin and microtubule cytoskeleton, in response to diffusible guidance factors have raised an increasing attention. We will here review the role of guidance cues involved in PCN migration in particular netrin-1, Slit and Nr-CAM. We will also consider Rho-GTPases that have been proposed to mediate axon outgrowth and neuronal migration, especially in response to netrin-1, and which may act as a relay between extracellular signals and intracellular remodeling. Recent findings from in vitro pharmacological inhibition of various Rho-GTPases and over-expression of effectors bring molecular cues that, in accordance with anatomical data, fit the idea that nucleokinesis and axon outgrowth are not strictly coupled events during PCN migration.

Theme: Development and regeneration
Topic: Axon guidance mechanisms and pathways—cell differentiation and migration

Keywords: Nucleokinesis; Cytoskeleton; Tropism; Floor-plate; Slit; netrin-1; Rho-GTPase

Contents

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doi:10.1016/j.brainresrev.2005.01.003

1. Introduction

1.1. The precerebellar system: an appropriate model to study axon pathfinding and neuronal migration during tangential migration

A basic property of immature neurons in the developing nervous system is their ability to migrate from their birthplace in proliferative zones of the developing brain to their final location in the adult brain. The precerebellar system, located in the hindbrain, provides the principal input to the cerebellum and is essential for coordinated motor activity. Precerebellar young postmitotic neurons undergo subsequent long distance tangential circumferential migration from the germinal neuroepithelium (rhombic lip; Fig. 1A) to their final position in the adult hindbrain. Neurons emit a leading process and each cell nucleus of the migrating cell moves within its own leading process through a neurophilic migration, i.e. nucleokinesis (Fig. 1B). Derivatives from rostral and caudal rhombic lips are quite diverse. The dorsalmost region of the rostral hindbrain differentiates not solely as cerebellar granule neurons but also gives rise to isthmic neurons [64,100] and to other rostral hindbrain neurons, including the locus coeruleus, the reticularis pontis and basal pontine gray (PN) nuclei [5,57]. The different populations of precerebellar neurons (PCN) that are derivatives from the caudal rhombic lip include, among others, external cuneatus (EC), lateral reticular (LR) and inferior olivary (IO) nuclei. In the present review, we will focus on these PCN since most molecular data have been recently reported for PCN from the caudal rhombic lip. PCN present overlapping proliferation periods from the upper to the lower rhombic lip [93]. Nevertheless, they show quite distinct tangential migratory pathways and final localizations and their intrinsic characteristics have been anatomically well-documented [4,15,40]. Thus, PCN provide an appropriate comparative model to study decisions that govern the neuronal specification. The migration of ION occurs through the submarginal stream [3,4,13,14] whereas other PCN migrate through the marginal stream (Figs. 1C–D). Axons of *all* PCN first cross the floor-plate–a ventro-medial glial structure that extends all along the antero-posterior axis of the CNS–and then reach their cerebellar entry whereas their somata do not respond to signals secreted by the floor-plate in the same way: the cell bodies of LRN/ECN cross the floor-plate and continue their translocation until they reach their final location in the contralateral hindbrain contrary to ION cell bodies that stop before crossing the floor-plate although their axons have already crossed the latter (Figs. 1C–D).

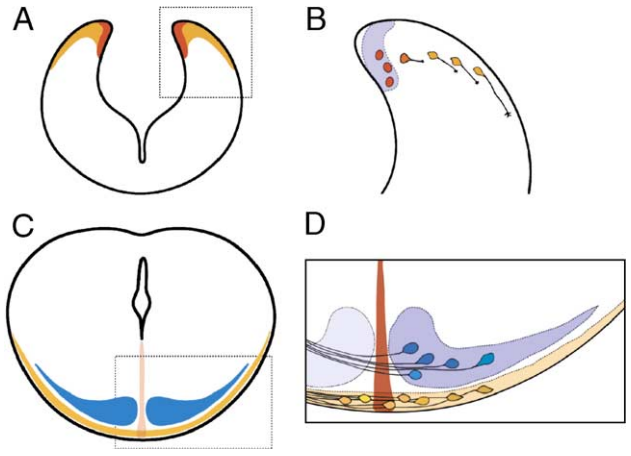

Fig. 1. Migration of precerebellar neurons. ION and LRN/ECN progenitors proliferate in the rhombic lip (in red) and start their migration respectively around E11 and E12 in the hindbrain (in yellow). (B) Schematization of rhombic lip and of the initial migratory stream of PCN at higher magnification. Postmitotic neurons (in yellow) first emit a leading process. Then, nucleus and organites translocate within the leading process through a mechanism named nucleokinesis. (C) At E13, ION (in blue) reach the ventral regions of the ventral hindbrain and their cell bodies stop before crossing the floor-plate. Conversely, LRN (in yellow) still migrate across the floor-plate to locate contralaterally to their site of genesis. (D) Higher magnification of schema C. ION axons cross the floor-plate whereas cell bodies (in blue) stop when reaching it. Both LRN/ECN axons and cell bodies (in yellow) cross the floor-plate.

These observations suggest that the floor-plate, an intermediate target for those migrating neurons, or the cerebellum, the ultimate target, contain or release signals that affect olivary neurons differently from other PCN (Fig. 1D). Mechanisms of nuclear translocation are likely to be different, at least partially, from those that govern the pathfinding of the leading process itself since there is no absolute coupling between both phenomena, at least for ION. The analysis of Rho-GTPases involved in PCN migration in vivo and in vitro has underlined that axon outgrowth and nuclear migration were not strictly dependent events since axon outgrowth could occur when nucleokinesis was blocked whereas nuclear migration could occur when axon elongation was affected [21].