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Facial motor neuron migration advances

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During development, the migration of specific neuronal subtypes is required for the correct establishment of neural circuits. In mice and zebrafish, facial branchiomotor (FBM) neurons undergo a tangential migration from rhombomere 4 caudally through the hindbrain. Recent advances in the field have capitalized on genetic studies in zebrafish and mouse, and high-resolution time-lapse imaging in zebrafish. Planar cell polarity signaling has emerged as a critical conserved factor in FBM neuron migration, functioning both within the neurons and their environment. In zebrafish, migration depends on specialized 'pioneer' neurons to lead follower FBM neurons through the hindbrain, and on interactions with structural components including pre-laid axon tracts and the basement membrane. Despite fundamental conservation, species-specific differences in migration mechanisms are being uncovered.

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Introduction

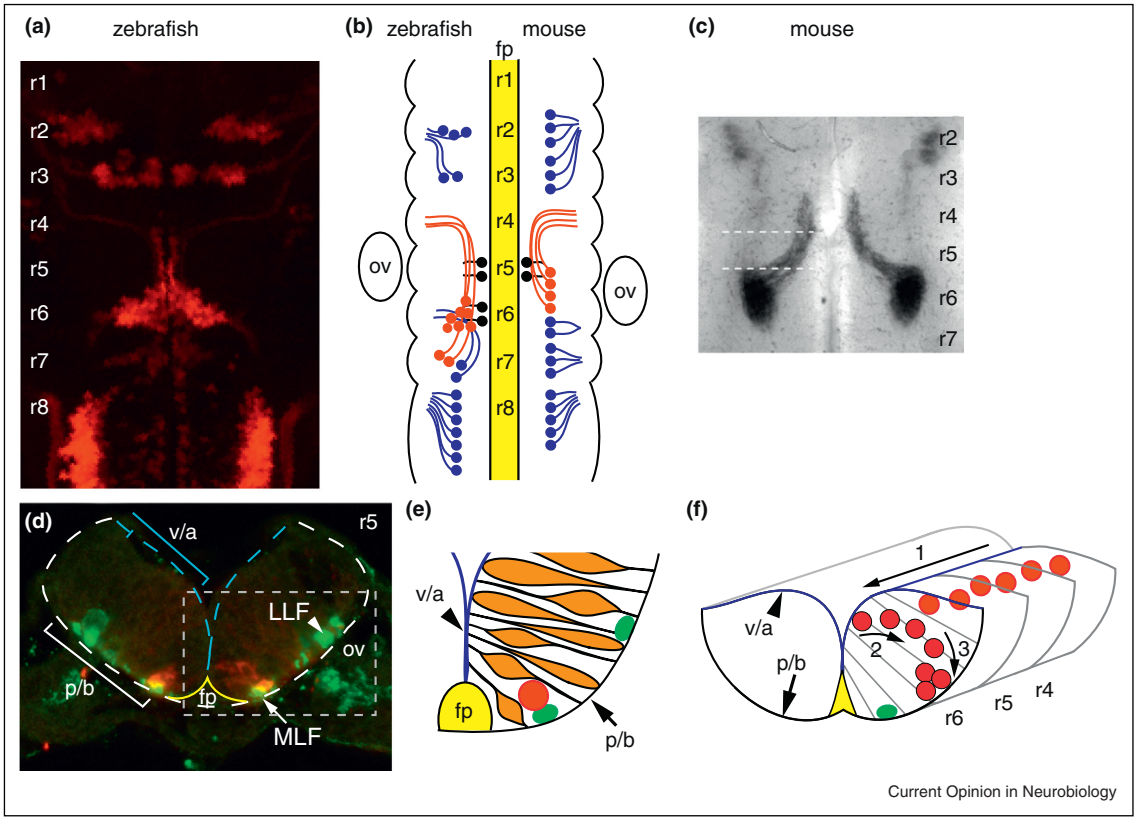
The development of the vertebrate brain is a complex process, in which the construction of brain architecture and intricate neural circuitry are effectively coordinated. One aspect of this process is the migration of neurons from their birth-places in the ventricular zone, to establish laminar or nuclear structures. Defective neuronal migration underlies several devastating neurological syndromes including lissencephalies (see article in this issue), and intractable forms of epilepsy [1]. Local radial migration is common, but in addition, specific neuronal types undergo longer distance tangential migrations, orthogonal to the plane of the neuroepithelium [2–4]. Here we focus on the tangential migration of FBM neurons, where extensive characterization is providing insights that may be more broadly applicable.

The FBM neurons form the motor component of the facial (VIIth cranial) nerve, which innervates second pharyngeal arch derivatives including facial muscles. Damage or deficits to the facial nerve are associated with syndromes and neuropathies such as Bell's Palsy [5] and Möbius syndrome [6]. Cranial motor neurons originate in specific rhombomeres of the segmented vertebrate hindbrain ([7]; Fig. 1), and follow stereotyped migration pathways to coalesce into motor nuclei. Caudally directed migration of FBM neurons occurs in humans, mice and fish, but is minimal in chickens [7,8]. FBM neurons are born at the ventricular surface of ventral rhombomere 4 (r4) and extend axons via an r4 exit point into the facial nerve (Fig. 1). The FBM neuronal cell bodies migrate caudally adjacent to the medial floor plate into r6 (mouse) and r6/7 (zebrafish). In all species, the caudal migration appears to be a somatal translocation, independent of guidance by radial glia. The position that the neurons occupy during their caudal migration differs between zebrafish and mouse: in zebrafish, caudal migration follows a brief ventral migration to the pial surface of the neural tube (Fig. 1D and E), whereas in mice the neurons migrate closer to the ventricular surface [11•,12] (Fig. 1F). Upon reaching their destination, FBM neurons undergo a lateral migration, away from the floor plate, to form nuclei (reviewed by [9,10]). In mice a final phase of radial migration is also required, from the ventricular to the pial surface, which is disrupted by mutations in *reelin* and *Dab1* [13] and likely occurs along radial glia. During migration, the facial motor axons are laid down behind the migrating neurons, forming a loop around the abducens nucleus (VIth nerve) to produce the internal genu (bend) of the facial nerve.

The role of intrinsic and extrinsic factors in FBM neuron migration

The migratory capacity of FBM neurons is an aspect of their regional identity, governed by an interplay between intrinsic and extrinsic factors (summarized in Table 1). Transcriptional regulatory networks specify FBM neurons, with anteroposterior and dorsoventral patterning information converging via *Hox* and *Nkx2.2* genes to regulate in particular the expression of *Phox2b* [14]. *Hoxb1*, which is highly expressed in r4, is an important player, conferring migratory capacity on FBM neurons via downstream targets [12,15–19]. Mice mutant for the Hoxb1 targets *Gata3* and *Tbx20* lack FBM migration, and knockin approaches have revealed a specific role for *Phox2b* [19]. Rohrschneider and colleagues [20] identified zebrafish *prickle1b* (*pk1b*) as a *Hoxb1a*-regulated gene with elevated expression in FBM neurons. Ectopic expression of *pk1b* in r2-derived trigeminal BM neurons

Figure 1



Zebrafish and mouse facial branchiomotor neuron migration. (**a**) Dorsal view of zebrafish branchiomotor neurons (BMNs) in an Tg[*isl1:GFP*] (red) transgenic embryo, 48hpf. Rhombomere (r) number is indicated. (**b**) Schematic rendering of zebrafish (48hpf) and mouse (12.5 dpc) BMN organization in dorsal view, anterior to the top. FBM neurons in red, other BM neurons in blue, abducens motor neurons in black; ov, otic vesicle; fp, floor plate (yellow). (**c**) Dorsal view of a mouse embryo labeled by in situ hybridization with *Islet-1*, highlighting the trigeminal (in r2) and FBM neurons at 12.5 dpc. (**d**) Transverse section of a zebrafish embryo at the level of r5 at 24hpf, dorsal up. FBM neurons (red) are in close contact with the MLF (green, arrow). The pial or basal surface (p/b, dashed white line), ventricle or apical surface (v/a, dashed blue line), and floor plate (fp, yellow) are outlined. (**e**) Schematic of the ventral region of the zebrafish neural tube highlighted in d (gray box). FBM neurons (red) migrate caudally along the MLF (green) at the pial surface of the neural tube (arrow), adjacent to the floor plate (fp, yellow) and between endfeet of the neuroepithelial cells (orange) of the neural tube. The ventricle/apical surface is highlighted in blue (arrowhead) and the pial/basal surface is in black (arrow). (**f**) Schematic of FBM neuron (red) migration through the mouse hindbrain. Neurons migrate caudally (1) close to the ventricular surface; this is followed by lateral (2) and radial (3) migration in r6. The ventricle/apical surface is highlighted in blue (arrowhead) and the pial/basal surface is in black (arrow), floor plate in yellow.

(which normally migrate only laterally; Fig. 1) is sufficient to cause these cells to migrate caudally [21•], implying that neuron-intrinsic changes in gene expression can confer tangential migratory properties. Mapp *et al.* [21•] also demonstrated that Pk1b functions in the nuclei of FBM neurons to localize the transcriptional repressor Rest, suggesting that Rest represses terminal maturation genes to maintain the competence of FBM neurons to respond to migration cues [21•,22].

Intrinsic factors render FBM neurons competent to respond to external cues via regulation of a repertoire of receptors. While understanding of this regulation is limited, the neuronal membrane proteins Tag1, Ret and Cadherin8 are expressed during specific phases of mouse FBM migration, and deletion of transcription factor *Ebf1* leads to incorrect spatial regulation of these molecules [23]. Deletion of mouse *Tbx20* also alters expression of molecules in the planar cell polarity (PCP) pathway [9]. In addition, several receptors play important roles in FBM neuron migration, via interactions with their environmental ligands [24–26] (Table 1). For example, Vegf164 expressed in the caudal hindbrain exerts a chemoattractive effect on FBM neurons via Nrp1 [25], and Wnt5a-mediated chemoattraction may also be instructive in the caudal movement [27]. Whereas these receptors and ligands provide directional information, a variety of molecules and structural features also provide permissive cues; as yet the interactions between these factors remain elusive.

PCP signaling plays a key role in FBM migration

Recent studies have revealed the critical importance of PCP signaling in orchestrating FBM neuron migration.