Neural crest cells and motor axons in avians
Common and distinct migratory molecules

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It has long been thought that the same molecules guide both trunk neural crest cells and motor axons as these cell types grow and extend to their target regions in developing embryos. There are common territories that are navigated by these cell types: both cells grow through the rostral portion of the somitic sclerotomes and avoid the caudal half of the sclerotomes. However, these cell types seem to use different molecules to guide them to their target regions. In this Review, I will discuss the common and distinct methods of migration taken by trunk neural crest cells and motor axons as they grow and populate their target regions through chick embryos at the level of the trunk.

Introduction

Avian trunk neural crest cells originate in the dorsal neural tube, undergo an epithelial to mesenchymal transition (EMT) and migrate to their target regions where they give rise to a wide range of derivatives including sensory and sympathetic neurons, glia, pigment cells and cells of the adrenal medulla (see Fig. 1).1-3 Trunk neural crest cells have been a well-studied population of migratory cells that can be studied in vitro or in vivo. Evidence that they are guided to their target regions by molecular cues in the environment implicates fibronectin,4-6 laminin,7 integrins,8-10 members of the Eph family11-14 and many other molecules in establishing the avian migratory pattern through rostral, but not caudal, somitic sclerotomes (i.e., talin, vinculin, versican, tenascin). Most of these molecules have inhibitory effects but some of them are growth-promoting.

In contrast to trunk neural crest cells, avian motor neurons originate in the ventral neural tube and extend their processes or axons along complicated terrain to specific muscle targets in the axis or the hindlimb (see Fig. 1).

As they mature, motor neurons organize into columns including the medial portion of the medial motor column (MMC(m)) that makes a sharp turn next to the dorsal root ganglia and innervates axial muscles and the lateral motor column (LMC) that projects to and innervates limb muscles (see Fig. 1). Motor axons must find their way to their muscle targets precisely. In describing these cell types, a difference is already visible: trunk neural crest cells migrate as whole cells away from the dorsal neural tube, whereas motor neurons leave their cells bodies in the ventral neural tube and instead grow their processes or axons to target muscles. Avian motor neurons and/or their axons also express Eph family members,15-17 semaphorins and their receptors,18 fibronectin, laminin and integrin receptors.19,20

As trunk neural crest cells leave the dorsal neural tube, they migrate ventromedially and grow through rostral somitic sclerotomes, as well as dorsolaterally, between the ectoderm and somites.1 In a similar manner, motor axons grow through rostral (anterior) somitic sclerotomes.21 Thus, both cell types avoid caudal (posterior) somitic sclerotomes. Therefore, for this portion of their migration or extension, trunk neural crest cells and motor axons travel similar or common pathways.

Results

There is one case where it has been examined in vivo in chick whether trunk neural crest cells and motor axons use the same molecules during their migration.22 Koblar and colleagues were investigating whether members of the Eph family (i.e., Eph receptor tyrosine kinases and their ligands, the ephrins) guided both trunk neural crest cells and motor axons. Using the same fusion proteins that were used previously to disrupt trunk neural crest migration,22 Koblar and colleagues found that although the patterning of trunk neural crest cells was disrupted and trunk neural crest cells were found in the rostral and caudal somitic sclerotomes, they could not alter the patterning of motor axons and they were found instead normally, in rostral somitic sclerotomes (Fig. 2). Importantly, their results suggest that in vivo neural crest cells and motor axons at trunk levels used distinct molecules to guide their growth through rostral somitic sclerotomes to their target regions.

The explanation for their findings likely comes from the territory from which the different cell types migrate, the Eph receptors expressed differentially by trunk neural crest and motor neurons/their axons, and which cells they migrate through. In one scenario, trunk neural crest migrate away from the dorsal neural tube. In another scenario, motor neurons extend their axons from the ventral neural tube. There are differences in the expression of Eph receptors by trunk neural crest and motor neurons/their.
Figure 1. Patterns of migration and growth from trunk neural crest cells and motor axons. 
(A) Trunk neural crest cells originate from the neural plate (NP), and after it undergoes folding, becomes a neural tube (NT). Trunk neural crest cells migrate from the dorsal neural tube and are indicated in gray. 
(B) Motor neurons form in the ventral neural tube and extend axons to the periphery. 
(C) To view trunk neural crest cells and motor axons navigating along the body axis, a schematic diagram is shown. Trunk neural crest cells migrate on two pathways to their target regions: 
(1) a dorsolateral pathway between the ectoderm and somites where these neural crest cells give rise to pigment cells and 
(2) an ventromedial pathway through the anterior (rostral) sclerotomes but not the posterior (caudal) sclerotomes.
axon growth. Semaphorins interact with their receptors neuropilins and plexins and come in two forms: a transmembrane form or soluble form. The expression of semaphorins in avians during trunk neural crest migration has not been reported. Motor axons in mice use semaphorins but in this case, semaphorins have effects on motor axon growth. It is not clear whether semaphorins expressed by boundary cap cells (derivatives of neural crest) or motor axons are defective in mouse mutants. It is clear that motor axons grow through the rostral sclerotomes but it is not known that both neural crest cells and motor axons at the same level use the same semaphorins or their receptors to navigate to their target regions in chick or in mouse.

Fibronectin, laminin and their integrin receptors have also been implicated in the migration of trunk neural crest cells in vitro. The notion is that these factors promote migration of trunk neural crest cells through the rostral sclerotomes. However, mice lacking these factors don’t have defects in trunk neural crest migration or motor axon outgrowth, suggesting that other factors or molecules are involved. On one hand, there may be genetic differences between mouse and chick. However, to date, these experiments in vivo have not been performed in chick.

There have been recent studies in cranial neural crest cells that have important implications for motor axon pathfinding. One study shows that in mice, EphB and ephrin-B2 interactions are required for the thymus, a derivative of cranial neural crest cells, to migrate and form in its correct location. Apparently, in mice that lack ephrin-B2 in cranial neural crest cells, thymi don’t form at their proper location, although they generate T cells and apparently function normally. Do the same receptors and ligands work in chick to provide for the correct migration and formation of the thymi? These experiments must still be done but the expression of Eph family members has been accomplished. Importantly, these experiments suggest that Eph family members influence the formation of motor or motor/sensory cranial ganglia. Although these experiments have been performed in the chick, there remains much more to do.

**Discussion**

Eph family members play a key role in establishing migratory patterns in trunk neural crest cells as well as cranial neural crest cells. Disruptions using fusion proteins always result in the migration of trunk neural crest cells into the rostral and caudal somitic sclerotomes. However, the same disruptions do not result in motor axons being mispatterned. Motor axons leave the neural tube normally and navigate to their target muscles. What do the results of these experiments imply? There are different members of the Eph family involved in patterning trunk neural crest cells and motor axons. Our analysis reveals that trunk neural crest cells that migrate ventromedially express EphB receptors and respond to ephrin-B1 in the caudal somitic sclerotomes whereas motor neurons from the MMC(m) and their axons express EphA4 and ephrin-A.

Results thus far demonstrate that some of the semaphorins and their receptors, fibronectin, laminin and their integrin receptors play central roles in trunk neural crest migration and/or motor axon growth. But the experiments have not been done in vivo that allow investigators to proclaim that these molecules work in both processes of trunk neural crest cell migration and motor axon outgrowth through somitic sclerotomes. Mice have been made that lack these factors but what works in mice may not be the same in chicks, zebrafish, flies or nematodes.

In conclusion, there are a number of reasons to believe that different molecules influence trunk neural crest cells and motor axons as they grow through the rostral somitic sclerotomes in avians. It may be that different combinations of Eph family members also influence cranial neural crest migration and the formation of motor and motor/sensory ganglia versus trunk neural crest cells and motor axons that grow through the rostral somitic sclerotomes. I predict that distinct molecules influence these plethora of different cell types, but we will have to wait and see.

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