EphA4 and ephrin-A interactions in avian neural crest cell segmentation

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Table of Contents

Abstract

The patterned migration of NC cells through the rostral half-somite contributes to the overall segmental arrangement of the peripheral nervous system. The Eph family of receptor tyrosine kinases and their interacting partners, the ephrins are involved in a vast array of morphogenetic processes during development including remodelling of the vasculature, axon guidance, and boundary formation. Functional blocking experiments have shown that Eph/ ephrin-B interactions are key mediators of neural crest cell segmentation. In addition, ephrin-A proteins have been described on the dorsal root ganglion and EphA7 in the caudal somite-half. Thus, the aim of this research was to further investigate the distribution of EphA/ ephrin-A proteins during peripheral nervous system segmentation in the trunk. Expression studies revealed that EphA4 and ephrin-A5 had a dynamic distribution with respect to neural crest cell migration, suggestive of a guidance role. Whilst ephrin-A5 was expressed on neural crest cells throughout their ventromedial migration, EphA4 was expressed both on and around neural crest cells during their intial migration into the rostral half-somite and then later defined neural crest avoidance zones in this tissue.

To test the possible role(s) of EphA4 in neural crest cell development, EphA4 was mis-expressed in the dorsal neural tube and subsequently on neural crest cells during their migration through the somite. Over-expression of EphA4 perturbed the segmental migration of neural crest cells, causing them to form aggregates at the dorso-medial neural tube. In the neural tube, EphA4 over-expression facilitated cell clustering and a non cell-autonomous inhibition of epithelio-mesenchymal-transition. Reduction of kinase-dependent EphA4 signalling enhanced neural crest cell motility leading to their premature emigration from the neural tube and migration into incorrect territories such as the caudal half-somite. Analysis of the cellular basis of EphA4 effects on NC cell EMT established that the cytoskeleton was a primary target for EphA4 activity during EMT. In addition, EphA4 over-expression produced a morphology indicative of enhanced cell-cell adhesions possibly through cadherin-mediated junctions. In summary, these data point to a novel role for EphA4 in negatively regulating the adhesive and/or cytoskeletal changes required for successful neural crest cell EMT. A model is suggested whereby the dynamic balance between ephrin-A-mediated signalling pathways, (that promote EMT) and EphA4-mediated regulation, (that inhibits EMT) provides a pivotal link between noggin/BMP4 activity and cellular changes required for delamination.