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Review

Expression and function of cell adhesion molecules during neural crest migration

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ABSTRACT

Neural crest cells are highly migratory cells that give rise to many derivatives including peripheral ganglia, craniofacial structures and melanocytes. Neural crest cells migrate along defined pathways to their target sites, interacting with each other and their environment as they migrate. Cell adhesion molecules are critical during this process. In this review we discuss the expression and function of cell adhesion molecules during the process of neural crest migration, in particular cadherins, integrins, members of the immunoglobulin superfamily of cell adhesion molecules, and the proteolytic enzymes that cleave these cell adhesion molecules. The expression and function of these cell adhesion molecules and proteases are compared across neural crest emigrating from different axial levels, and across different species of vertebrates.

Contents

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Introduction

Neural crest (NC) cells migrate extensively before giving rise to a variety of cell types. NC cell–cell and cell–matrix interactions are an essential part of the migration process. In fact, NC cell migration depends on optimal levels of adhesion, as too little or too much adhesion result in migration defects (Anderson et al., 2006b). In this review, we describe how the immunoglobulin superfamily of cell adhesion molecules (IgCAMs), cadherins and integrins, and the proteolytic enzymes that cleave them, regulate the migration of NC cells arising from different regions of the neural axis.

NC cells form at the junction of the neural plate and epidermal ectoderm during neurulation. The formation of the NC requires multiple signaling pathways and transcription factors to establish a pool of pre-migratory neural crest cells at the dorsal most regions of the neural folds (Betancur et al., 2010). Once NC cells have formed, they undergo an epithelial–mesenchymal transition (EMT) in order to migrate away from the neural tube. They begin migration from the dorsal part of the neural tube prior to, during or after the closure of the neural tube, depending on the axial level and species. Cell adhesion molecules play roles in NC EMT, migration and also in their aggregation at their final destination, but in this review we focus primarily on the expression and function of cell adhesion molecules during NC migration. Changes in cell–cell adhesion, cell–matrix adhesion and the cell cytoskeleton during EMT have been reviewed recently (Clay and Halloran, 2011; Taneyhill, 2008; Thiery et al., 2009).

NC cells from different anteroposterior axial levels follow different migratory pathways and give rise to different derivatives (Le Douarin and Kalcheim, 1999; Fig. 1). The main sub-divisions of the neural crest are cranial, vagal and trunk. In this review, we discuss the role of cell adhesion molecules in regulating the migration of each of these NC populations. The expression and function of the main cell adhesion molecules are summarized in Table 1.

Cranial neural crest

Cranial NC cells give rise to much of the cartilage and bone of the skull and face, as well as other connective tissues, and contribute to neurons and glia in cranial ganglia. The cranial NC arise from the midbrain to somite 5 and migrate underneath the ectoderm in a ventral direction to populate the frontonasal process, branchial arches, and the trigeminal and epibranchial ganglia. While there is some intermingling of NC cells arising from different anteroposterior levels (Kulesa and Fraser, 1998), NC cells from particular axial levels follow pathways to populate corresponding facial processes (Lumsden et al., 1991; Sadaghiani and Thiebaud, 1987; Trainor et al., 2002). Particular cranial regions express inhibitory molecules and repel NC cells, narrowing the migratory pathways of NC from certain axial levels (Farlie et al., 1999; Golding et al., 2004). The earliest migrating cells populate the facial processes and give rise to mesenchymal derivatives, while later migrating NC cells remain in more dorsal regions and contribute to cranial ganglia (Baker et al., 1997).

In contrast to other vertebrate species, the initial migration of cranial NC in *Xenopus* is a collective migration, followed by a wave of single cell migration (Alfandari et al., 2003). This collective migration process involves contact inhibition of locomotion in which protrusions of NC cells collapse when they contact another NC cell (Carmona-Fontaine et al., 2008), and collective chemotaxis, mediated by the chemokine SDF1 (Theveneau et al., 2010). In other vertebrates, such as such as chick, time-lapse imaging revealed that many NC cells migrate to the branchial arches in dynamic chains (Kulesa and Fraser, 1998, 2000). Within these chains, the NC cells are in nearly constant contact with each other over short and long distances via lamellipodia or filopodia (Teddy and Kulesa, 2004). Moreover, some migrating cranial NC exchange cytoplasmic material through thin cellular bridges (McKinney et al., 2011). Cell–cell adhesion is involved in each of these modes of migration, and while *N*-cadherin has been implicated in contact inhibition of locomotion in *Xenopus*, the molecular mechanisms involved in chain migration have not yet been identified (Alfandari et al., 2010; Teddy and Kulesa, 2004; Theveneau et al., 2010).

Cadherins

The cadherin superfamily is divided into subfamilies, and of these, type I and type II classical cadherins, and also protocadherins have been implicated in NC development and migration. These cadherins are transmembrane molecules that extracellularly undergo primarily homophilic binding to mediate cell–cell adhesion (Gumbiner, 2005). The strength of the cell–cell adhesion differs between cadherins: type I cadherins promote stronger adhesiveness than type II cadherins (Chu et al., 2006). In addition, some cadherins are also able to bind other molecules extracellularly (Gumbiner, 2005). Intracellularly, classical cadherins interact with catenins, while protocadherins can interact with Fyn kinases, each of which has signaling roles and various effects on cell behavior (Gumbiner, 2005). The role of cadherins in mediating cell adhesion is complex and can be regulated at many levels, both intracellularly and extracellularly (Halbleib and Nelson, 2006). Cadherins are involved in NC EMT, migration of cranial NC and the aggregation of cranial ganglia.

Cadherin 6B, a type II cadherin, is expressed by avian premigratory NC (Nakagawa and Takeichi, 1995), and is transcriptionally downregulated by Snail2 prior to emigration (Taneyhill et al., 2007). Cadherin-6B plays a role in the EMT undertaken as NC begin to migrate (Coles et al., 2007; Taneyhill, 2008). Inhibition by morpholino of cadherin-6B in chick embryos *in ovo* promoted premature and increased migration of the cranial NC, while overexpression reduced the number of migrating cranial NC and increased ectopic NC in the neural tube lumen *in vivo*, but not *in vitro* (Coles et al., 2007). These findings are different from the effect of manipulation of cadherin-6B in trunk NC (see below).

Expression of the type I *N*-cadherin by migrating avian cranial NC *in vivo* has not been detected using antibody labeling (Bronner-Fraser et al., 1992b; Duband et al., 1988); however, it has been detected by qPCR (McLennan et al., 2012). A possible explanation for this discrepancy is that processing for immunofluorescence may only allow visualization of *N*-cadherin associated with adherens junctions, and *N*-cadherin in migrating NC *in vitro* is mostly soluble and not associated with cell–cell contacts (Monier-Gavelle and Duband, 1995). In contrast, during early cranial NC migration in *Xenopus* embryos *N*-cadherin mRNA and protein can be detected (Theveneau et al., 2010), and both overexpression and morpholino knockdown of *N*-cadherin *in vivo* block cranial NC emigration (Theveneau et al., 2010). *In vitro* studies demonstrated a role for *N*-cadherin during cranial NC collective migration in *Xenopus*. Function blocking antibodies to *N*-cadherin prevented contact inhibition of locomotion and collective polarization of cranial NC cells toward an SDF1 gradient (Theveneau et al., 2010). Interestingly, cranial NC cells treated with an *N*-cadherin morpholino were highly motile in culture, and dispersed more rapidly than control cells (Theveneau et al., 2010). This behaviour is similar to migratory cardiac NC from *N*-cadherin null mutant mice, which have increased speed and persistence of movement *in vitro*, but decreased directionality (Xu et al., 2001). A model of *Xenopus* cranial NC migration has been proposed, in which *N*-cadherin-mediated cell adhesion causes contact-dependent cell