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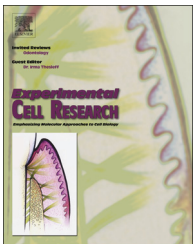

Review Article

Cranial neural crest: Migratory cell behavior and regulatory networks

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ABSTRACT

Defects of the head and neck region account for a substantial portion of all human birth disorders. The high incidence of malformations in this region may be attributed in part to the intricate means by which the facial region is assembled during embryonic development. The starting constituent for the majority of skeletal and connective tissues in the face is a pluripotent population of cells, the cranial neural crest (CNC) cells. This population of cells exhibit remarkable migratory abilities and diversity of potential cell types. This review draws on extensive research that has been done in the field, focusing specifically on findings generated in the last decade on cell behavior and the gene regulatory networks of migratory CNC cells. In the later part of this review, the importance of the CNC cells in the overall development of the craniofacial region will be illustrated with a discussion of a craniofacial birth defect, the Treacher Collins syndrome. The next decade will most likely herald in an era of greater understanding of the integrative molecular networks at different stages of the development of the CNC cells. Such new information is essential towards a better understanding the etiology and pathogenesis of the many craniofacial birth defects and will ultimately lead to new therapeutic modalities.

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Introduction

Malformations involving the facial regions account for at least one third to half of all human birth defects [1,2]. The high incidence of malformations in this region is attributed to the intricate means by which the facial region is assembled during embryonic development. The starting constituent for the majority of skeletal and connective tissues in the face is a pluripotent population of cells, the cranial neural crest (CNC) cells.

The neural crest (NC) cells originate at the boundary between neural and non-neural ectoderm along the antero-posterior length of the developing embryo before or shortly after neural tube closure [3,4]. CNC cells arise at the cephalic region from the forebrain, the midbrain and hindbrain and subsequently migrate away from their site of origin to colonize the regions of the developing craniofacial region (Fig. 1a). CNC cells formed from the forebrain and rostral midbrain colonize the frontonasal and periocular regions; from the caudal midbrain, they populate the maxillary component of the first branchial arch; and, in the hindbrain region, CNC cells emigrate from seven distinct segments known as rhombomeres (r in Fig. 1a). The CNC cells eventually contribute to the skeletal system (cartilages and bones of the jaws, middle ear and neck) (Fig. 1b), cranial nerves and ganglia in addition to several other structures such as the smooth muscles, connective tissues of the blood vessels, and dermis of the head. CNC cells also form multiple parts of the teeth through sequential and inductive epithelial–mesenchymal interactions between CNC-derived odontogenic mesenchymal cells and the overlying ectoderm (Fig. 1c). For example, the dentin and cementum are deposited and mineralized by CNC cell-derived odontoblasts and cementoblasts, respectively. Aberrations in any stages of the formation, migration and differentiation of this population of cells are the main causes of many of the craniofacial birth disorders found in humans (reviewed in [5]). There is therefore strong interest in this population of cells in the scientific community, as evidenced by the extensive research performed in this area in the last few decades and in the number of excellent recent review papers [6–11], to which the reader is encouraged to refer.

This review will focus on some of major findings in the field of CNC research in the last half decade or so. In particular, we will highlight research that has increased our understanding of possible mechanisms adopted by CNC cells in their directed migration towards their final destinations. We will also discuss recent work on the network of genes utilized by migratory CNC cells, focusing on the genomic region of *Sox10*. In the later part of this review, the importance of the CNC cells in the overall development of the craniofacial region will be illustrated with a discussion of a craniofacial birth defect, the Treacher Collins syndrome. A brief discussion of future directions in neural crest research concludes the review.

Cell behavior of migratory cranial neural crest

NC cells have been shown to be induced as early as during gastrulation during embryonic development [12]. Specification and induction of the NC cells from the neuroepithelium occur as a consequence of multiple signals (reviewed in [13]). After induction at the neuroepithelium, the NC cells change from a pseudoepithelial

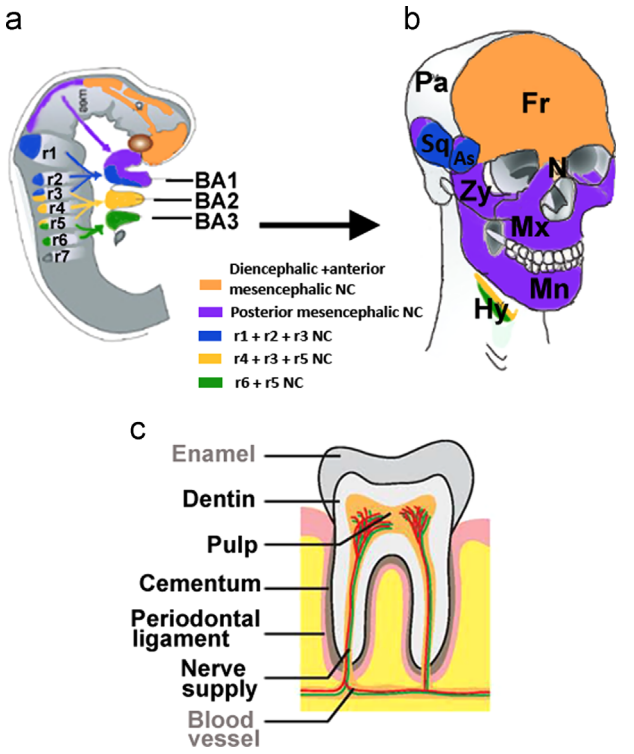

Fig. 1 – Migration and skeletal and dental fates of the cranial neural crest cells. (a) Embryo showing the colonization of the head and pharyngeal arches by fore-, mid- and hindbrain neural crest cells. There are 7 distinct segments in the hindbrain known as rhombomeres (r), from which crest cells emigrate in three major paths to the branchial arches (BA) (three streams of migration color coded in blue, yellow and green). (b) Skull drawing shows comparative contributions of NC populations to cranial skeletal elements of human, with major bones coded to match the origin of the contributing migratory neural crest streams. (c) Most of the differentiated tooth tissues are derived from cranial neural crest cells (labeled in bold letters), except for the enamel and the blood supply. Adapted from Santagati and Rijli (2003) [51]. Fr=Frontal, Pa=parietal, N=nasal, Zy=zygomatic bones, Mx=maxilla, Mn=mandible, Sq=squamosal bone, As=alisphenoid, Hy=hyoid, r=rhombomere, BA=branchial arch.

state to a mesenchymal phenotype in a series of molecular events termed epithelial–mesenchymal transition (EMT) [14–18], delaminate and start migrating.

In a process unparalleled in its extent compared to any other embryonic cell types in vertebrate embryo, NC cells undergo migration. Migration of the CNC cells is directed, along well-defined routes, eventually ending in the ventral part of the brain and branchial arches [3–5]. They migrate first as a continuous wave and quickly split into three discrete segregated streams, predominantly from rhombomeres (r) 2, 4 and 6 to populate the first, second and third branchial arches, respectively (Fig. 1) (reviewed in [19]). The CNC cells have to move through an environment that comprises other CNC cells and cells of the neural, facial, and pharyngeal epithelia and cephalic mesoderm. Several molecular cues found within the local microenvironment