EXPERIMENTAL CELL RESEARCH 325 (2014) 138–147

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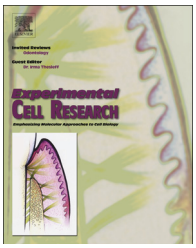

Review Article

Neural crest cell signaling pathways critical to cranial bone development and pathology

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ARTICLE INFORMATION

Article Chronology:
Received 30 December 2013
Accepted 17 January 2014
Available online 6 February 2014

Keywords:
Neural crest
Development
BMP
Wnt
Hedgehog
Craniofacial anomaly

ABSTRACT

Neural crest cells appear early during embryogenesis and give rise to many structures in the mature adult. In particular, a specific population of neural crest cells migrates to and populates developing cranial tissues. The ensuing differentiation of these cells via individual complex and often intersecting signaling pathways is indispensible to growth and development of the craniofacial complex. Much research has been devoted to this area of development with particular emphasis on cell signaling events required for physiologic development. Understanding such mechanisms will allow researchers to investigate ways in which they can be exploited in order to treat a multitude of diseases affecting the craniofacial complex. Knowing how these multipotent cells are driven towards distinct fates could, in due course, allow patients to receive regenerative therapies for tissues lost to a variety of pathologies. In order to realize this goal, nucleotide sequencing advances allowing snapshots of entire genomes and exomes are being utilized to identify molecular entities associated with disease states. Once identified, these entities can be validated for biological significance with other methods. A crucial next step is the integration of knowledge gleaned from observations in disease states with normal physiology to generate an explanatory model for craniofacial development. This review seeks to provide a current view of the landscape on cell signaling and fate determination of the neural crest and to provide possible avenues of approach for future research.

Contents

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http://dx.doi.org/10.1016/j.yexcr.2014.01.019
0014-4827

Introduction

Neural crest cells are multi-potent cells that are transient during development. They emerge at the most dorsal aspect of the body around the time of neural tube closure and are thus named *neural crest*. Neural crest cells are formed on all axial levels, but those formed at craniofacial levels differentiate into several cell types contributing a large portion of adult craniofacial structures. Thus dysregulation during their development leads to congenital craniofacial disorders such as DiGeorge syndrome (also known as velocardiofacial syndrome and 22q11.2 deletion syndrome) and Treacher-Collins syndrome (mandibulofacial dysostosis) [1–3].

Signaling molecules such as growth factors play a critical role for cell fate determination, growth, differentiation, and survival. Genetic studies in both humans and model animals have revealed a number of growth factors and transcription factors regulated by growth factor signaling that are critical for development of cranial neural crest cells. In this review, we summarize recent progress on how growth factor signaling contributes to neural crest differentiation and to skull morphology. Due to limited space, we will not mention palatogenesis, another important craniofacial developmental process where neural crest cells play critical roles [4–6].

Origin of neural crest cells

Neural crest progenitor cells are induced at regions of ectoderm between the neural plate and non-neural ectoderm. These cells undergo epithelial–mesenchymal transition to migrate ventrally to give rise to several different tissues including the peripheral nervous system. Unlike trunk neural crest cells that migrate to relatively deep levels of the body, the cranial neural crest cells migrate superficially. Neural crest cells emerging in the cranial region are distinct from those in trunk because they will give rise to osteoblasts and chondrocytes in addition to other cell types that trunk neural crest cells can differentiate into [7–10].

At the time of NC induction, growth factor signaling via bone morphogenetic proteins (BMPs), fibroblast growth factors (FGFs), and Wnt play pivotal roles [11–14]. Along with other signaling pathways such as Delta/Notch, retinoic acid, Hedgehog, and endothelin, the downstream targets of these pathways are transcription factors such as Msx1/2, Pax3/7, Zic1, Dlx3/5, Hairly2, Id3, and Ap2. These processes specify a border between neural plate and non-neural ectoderm. Soon after specification of neural crest progenitors, these signaling pathways induce a second set of transcription factors including Snail2, FoxD3, Sox9/10, Twist, cMyc and AP2. The combination of these transcription factors is believed to control EMT, migration, and differentiation of neural crest cells [15,16].

Contribution of neural crest cells to skull bones

Craniofacial mesenchymal tissues have three origins: neural crest, paraxial mesoderm, and lateral mesoderm [17]. Cranial neural crest cells (CNCC) give rise to the majority of cranial bones and cartilage. The contribution of CNCC was initially investigated by performing chick–quail transplantation experiments [18,19]. These assays revealed that the more anterior cranial bones are derived from neural crest whereas the posterior portion is from paraxial mesoderm [17]. The neural crest-mesoderm boundary lies within the frontal bone (Fig. 1). In the mouse, the Cre-lox system has allowed us to genetically label specific cell populations in order to trace their lineage. A handful of genes was found to be expressed in a neural crest-specific manner such as *Wnt1* and protein zero (*P0*) and transgenic mouse lines that express Cre recombinase using these neural crest specific promoters have been generated [20–22]. These mice are used to label neural crest cell derived cells in combination with Cre-reporter mice. This can mark neural crest cells "permanently" even if they differentiate to other types of cells because the promoter used for the reporter is ubiquitously active. Using Wnt1-Cre transgenic mouse line, the

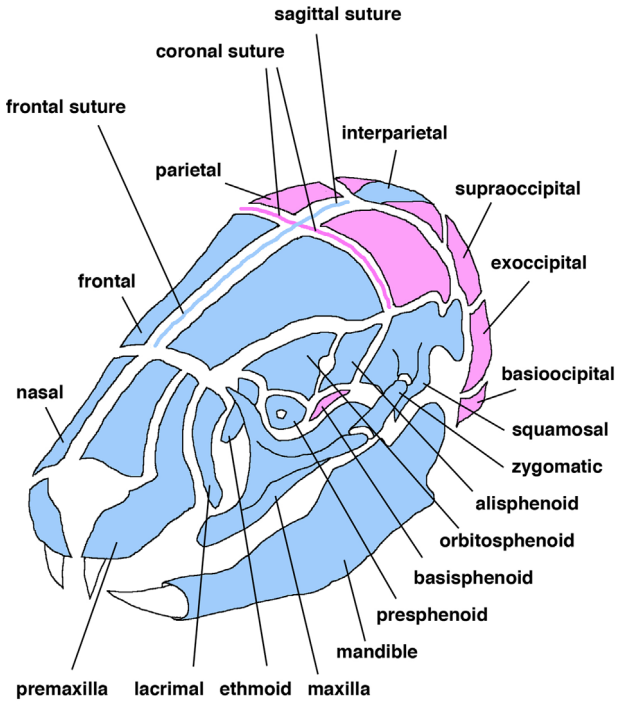

Fig. 1 – Origins of cranial bones and sutures. Blue indicates neural crest origin whereas pink indicates mesodermal origin. Not all bones comprising the cranial base are shown.