Neural Crest [1]

By: Barnes, M. Elizabeth Keywords: Arthur Marshall [2] Julia Platt [3] neural crest cells [4] neurocristopathies [5]

Early in the process of development, vertebrate embryos develop a fold on the neural plate [6] where the neural and epidermal ectoderms meet, called the neural crest [7]. The neural crest [7] produces neural crest cells [8] (NCCs), which become multiple different cell types and contribute to tissues and organs as an embryo develops. A few of the organs and tissues include peripheral and enteric (gastrointestinal) neurons and glia [9], pigment cells, cartilage and bone of the cranium and face, and smooth muscle. The diversity of NCCs that the neural crest [7] produces has led researchers to propose the neural crest [7] as a fourth germ layer, or one of the primary cellular structures in early embryos from which all adult tissues and organs arise. Furthermore, evolutionary biologists study the neural crest [7] because it is a novel shared evolutionary character (synapomorphy) of all vertebrates.

Although the neural crest [7] first appears in the embryo during gastrulation [10], the invagination and spreading process by which a blastula [11] becomes a gastrula [12], it becomes distinguishable during the neurula stage. The neurula-stage of development occurs when the neural plate folds and transforms into the neural tube [13], the structure that will eventually develop into the central nervous system [14]. The neural crest arises at two junctions, one on each side of the midline of the neural plate [6], between neural and non-neural ectoderm [15]. As neurulation [16] progresses and the neural tube [13] forms, the two junctions meet at the top of the neural tube [13]. Then the neural crest [7] separates from the neural tube, a process called delamination, and subsequently migrates away from the neural tube [13].

Some researchers argue that the interaction between the neural and epidermal ectoderm [15] stimulates the genesis of the neural crest [7]. However, most scientists treat the neural ectoderm [15] as the progenitor of neural crest cells, as the neural crest [7] gives rise to neurons and ganglia, the latter of which are bundles of neurons that lie on the periphery of the nervous system, outside the brain and the spinal cord. Furthermore, fate mapping [17] of neural crest cells [8] has also placed them in the neural ectoderm [15]. Researchers have studied NCCs because of the diversity of cell types that neural crest [7] gives rise to. For instance, NCCs provide a useful model for studying stem cells [18] because like stem cells [18], they have the potential to differentiate into a diverse number of cell types.

This graphic [19] displays how neural crest cells [8] form and migrate in different kinds of vertebrate animals.

Once the neural tube [13] is formed, the neural crest cells [8] (NCCs) differentiate into cardiac NCCs (CarNCCs), trunk NCCs (tNCCs), cranial NCCs (cNCCs), or vagal and sacral NCCs. The differentiation [20] subjects the NCCs to different chemical environments, ultimately resulting in their development into different cell types and tissues. First, the vagal and sacral NCCs migrate away from the neural tube [13]'s trunk through loosely packed cells, called mesenchyme [21], that are between the neural tube [13], epidermis, and somites [22] of the mesoderm [23]. These cells become gastrointestinal enteric ganglia and the parasympathetic ganglia of the neck. Some tNCCs migrate through one sub pathway that travels dorsolaterally into the ectoderm [15] and eventually to the midline of the belly, to pigment cells. Other tNCCs migrate laterally, eventually becoming a part of the developing brain, specifically sensory and sympathetic neurons, Schwann cells, and adrenomedullary cells. cNCCs develop into pigment cells, neurons, and glia [9] as well, but these are the only NCCs that contribute to the cartilage and bone of the face and skull. cNCCs are responsible for the development of the cartilage and connective tissue in the face as well as the thyroid glands. CarNCCs, on the posterior region of the neural crest, migrate dorsolaterally and form the septum of the pulmonary artery and the aorta, as well as the endothelium in the aortic arch arteries.

Researchers studied the neural crest [7] in the middle of the nineteenth century. In 1868, Wilhelm His [24], an embryologist in Basel, Switzerland, studying chick [25], or *Gallus gallus* [26] embryos, identified a layer of cells above the neural tube [13] as the progenitors of spinal and cranial ganglia. He called it the *Zwischenstrang* (intermediate cord). In 1874, His named it an organ-forming germinal region. However, what he identified was not the neural crest [7], but a subset of NCCs that had migrated from the neural crest [7] to a position above the neural tube [13]. Historians trace the first use of the term neural crest [7] to a paper published in 1879 by Arthur Marshall, a professor at Owens College in Manchester, England. In 1878, while also studying chick [25] embryos, he used the term neural ridge to describe the same cells that His had discovered above the neural tube [13], but he later revised his definition. Marshall coined the term neural crest [7] to describe the two junctions between the neural and epidermal ectoderm [15] that arise before the neural tube [13] is complete. He proclaimed that henceforth the term neural ridge should only be used to identify the band of cells that arise from the neural crest [7], which migrate above the neural tube [13] once neurulation [16] is

complete.

In 1893, Julia Platt identified NCCs from ectoderm [15] as the progenitors of cartilage in the face and in the pharyngeal arch skeletons of the teeth of mudpuppies (*Necturus maculosus* [27]). She researched at several institutions in the late nineteenth century, including the Marine Biological Laboratory [28], in Woods Hole, Massachusetts, and the University of Freiburg [29] in Freiburg, Germany. Many researchers rejected Platt's interpretation; partly because Germ Layer Theory, then an entrenched theory, claimed that each of the three germ layers [30] developed into the same kinds of structures across many kinds of organisms. Researchers claimed that Platt's theory of neural crest, and thus, ectoderm [15]-derived, pharyngeal arch skeletons, was impossible because skeletal tissues originated solely from the mesoderm [23]. Forty years later, in the 1920s and 1930s, researchers confirmed Platt's conclusion. In the 1950s, researchers began to further study skeletal tissues that developed from the neural crest [7].

In 1950, Sven Hörstadius published *The Neural Crest: Its Properties and Derivatives in the Light of Experimental Research*. In this monograph, which Hörstadius based on lectures given at the University of London in London, England, he reviewed experiments on the neural crest [7]. His review combined data from over two hundred and fifty papers. Hörstadius' work referred to experiments that verified Platt's conclusions, and it entrenched the neural crest as an area of biological investigation.

In the 1960s, neural crest [7] researchers examined how the trunk and cranial NCCs migrate and give rise to other tissues. In 1963 James Weston at Yale University [31] in New Haven, Connecticut, published "A Radioautographic Analysis of the Migration and Localization of Trunk Neural Crest Cells in the Chick." In that article, Weston argued that integumental melanoblasts migrated from the neural crest to the ectoderm [15]. In 1966, Malcolm Johnston, at the University of Rochester in Rochester, New York, published a similar study on cNCCs titled "A Radioautographic Study of the Migration and Fate of Cranial Neural Crest Cells in the Chick Embryo," in which he traced the end point of more NCCs, finding for example that some turned into connective tissues in the face. During the 1960s, researchers began to use avian embryos instead of the previously used amphibian embryos.

Researchers in the 1970s composed maps that chronicled the NCCs's movements. Researchers discovered that the different chemical environments in which NCCs originated caused them to differentiate into different kinds of cells and travel throughout the embryos. They also identified abnormalities in organisms that arise from defects in the development of the neural crest [7], called neurocristopathies.

In the 1980s, researchers discovered Hox genes [32], genes [33] that help cause embryos to develop according to major body axes. These genes [33] guide the migratory patterns of cells. Discovery of the Hox genes [32] allowed researchers to trace the molecular cause of different migration patterns of NCCs, leading to further subdivisions in the classification of NCCs. These classifications include the vagal and sacral NCCs that contribute to the enteric ganglia and neurons of the parasympathetic nervous system. Researchers also discovered that cardiac NCCs contributed to tissues in the developing heart.

Throughout the 1980s and 1990s, researchers compared the development of the neural crest [7] across taxa to test hypotheses about evolutionary ancestry. For example, biologists began to argue that vertebrates developed their distinctive hearts and heads only after their ancestors had evolved to have neural crests. This resulted in many publications, one of which is Carl Gans and Glen Northcutt's "Neural Crest and the Origin of Vertebrates [34]: a New Head," published in 1983 while the two worked at the University of Michigan [35] in Ann Arbor, Michigan. In this paper, Gans and Northcutt argue that vertebrates became vertebrates after a shift from passive to active modes of predation, concentrating many vertebrate features in the head.

Researchers began arguing that the neural crest [7] is a germ layer at the turn of the twenty-first century. Previously, researchers recognized three germ layers [30]: the ectoderm [15], mesoderm [23], and endoderm [36]. In 1999 Brian Hall [37], at Dalhousie University [38] in Nova Scotia, Canada, published *The Neural Crest And Neural Crest Cells In Vertebrate Development And Evolution*, in which he argued that the neural crest [7] meets the requirements to be a germ layer. First, he claims that germ layers [30] are defined as primary tissues from which an embryo develops. Hall notes that there are two types of germ layers [30], primary and secondary. The primary germ layers [30], the ectoderm [15] and endoderm [36] appear first in the developing vertebrate embryo, before fertilization [39]. Some animals, which scientists call diploblastic, have only these two germ layers [30]. This group includes organisms such as jellyfish and sponges. Tripoblastic animals, however, have a third germ layer, called mesoderm [23], which evolved in animals whose ancestors were diploblasts. These animals, called triploblasts, also belong to a group called bilateria, which includes flat worms [40] and humans [41], all of which have a primary axis of symmetry down the center of the body from head to tail.

Researchers consider the mesoderm [23] a secondary germ layer because it arises from the interactions of the first two germ layers [30]. Hall argues that like mesoderm [23], neural crest [7] is a secondary germ layer. He says that similar to the mesoderm [23], the neural crest [7] arises early in development from interactions in a primary germ layer, the ectoderm [15]. Also, it contributes to a large number of tissues and organs. Furthermore, the neural crest [7] is a vertebrate synapomorphy, like mesoderm [23] is a

bilaterian synapomorphy. Hall claims that the neural crest [7] appears after the evolution [42] of the tripoblasts. Therefore, he argues that the animals that came subsequently, the vertebrates, should be called tetrablastic, meaning four layers. Hall argues that because the neural crest [7] appears early in development, because it is ectodermal in origin, and because it is a vertebrate synapomorphy, it should be considered a secondary germ layer.

In the first decades of the twentieth century, researchers traced facial, pigment, heart, vision, and hearing abnormalities, including cleft palate and albinism, to an abnormal development of the neural crest and NCCs. Researchers also debated the properties of the mechanisms by which NCCs migrate. Furthermore, cancer researchers studied the neural crest [7] due to the similarity between NCCs and cancer cells. The mechanisms by which NCCs migrate during development, the specific signaling pathways, and transcription factors used by NCCs are the same as cancer cells, making NCCs a model for studying how cancer cells proliferate.

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Subject

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