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# Development of the autonomic nervous system: A comparative view

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ABSTRACT

In this review we summarize current understanding of the development of autonomic neurons in vertebrates. The mechanisms controlling the development of sympathetic and enteric neurons have been studied in considerable detail in laboratory mammals, chick and zebrafish, and there are also limited data about the development of sympathetic and enteric neurons in amphibians. Little is known about the development of parasympathetic neurons apart from the ciliary ganglion in chicks. Although there are considerable gaps in our knowledge, some of the mechanisms controlling sympathetic and enteric neuron development appear to be conserved between mammals, avians and zebrafish. For example, some of the transcriptional regulators involved in the development of sympathetic neurons are conserved between mammals, avians and zebrafish, and the requirement for Ret signalling in the development of enteric neurons is conserved between mammals (including humans), avians and zebrafish. However, there are also differences between species in the migratory pathways followed by sympathetic and enteric neuron precursors and in the requirements for some signalling pathways.



## 1. Introduction

With the exception of a small number of cranial parasympathetic neurons (Lee et al., 2003b), neurons and glial (support) cells of the peripheral autonomic nervous system arise from neural crest cells (NCC) (Le Douarin and Kalcheim, 1999). NCC are a transient population of cells that arise between the neural and non-neural ectoderm, undergo an epithelial-mesenchyme transition, and then emigrate from the dorsal neural folds around the time the neural folds are fusing to form the neural tube. The evolution of the neural crest, and its gene regulatory networks, have been the subjects of a number of recent reviews (Baker, 2008; Donoghue et al., 2008; Sauka-Spengler and Bronner-Fraser, 2008; Bronner-Fraser and Sauka-Spengler, in press; Holland, 2009; Nikitina et al., 2009). The basal chordate, *Amphioxus*, does not possess a neural crest (Nikitina et al., 2009), and so NCC have been thought to be an exclusively vertebrate trait. However, "neural crest-like" cells have been described in tunicates (Jeffery et al., 2004), and it has been proposed that NCC could have a longer evolutionary history than the vertebrates (Donoghue et al., 2008). Of the jawless vertebrates, lampreys have NCC and many parts of the neural crest gene regulatory network have been highly conserved (Sauka-Spengler et al., 2007; Sauka-Spengler and Bronner-Fraser, 2008). Recently, hagfish embryos have also been shown to possess NCC and variety of neural crest derivatives, including sympathetic ganglia (Ota et al., 2007; Kuratani and Ota, 2008).

Here we provide an overview of studies that have examined the development of the peripheral sympathetic, parasympathetic and enteric neurons in vertebrates. The comparative anatomy of the autonomic nervous system in adults is reviewed elsewhere (Nilsson, this issue). Abundant information about the development of autonomic neurons is available for laboratory mammals (particularly mice) and chick embryos. Information is rapidly accumulating for zebrafish, some descriptive and genetic data are available for humans, and limited data are available for amphibians, mainly *Xenopus*. However, to our knowledge there is negligible information available about the development of autonomic neurons in other extant classes of vertebrates including reptiles and cartilaginous fish.

## 2. Development of the sympathetic nervous system

### 2.1. Origin

Using quail-chick chimeras, sympathetic ganglia were shown to arise from NCC that emigrate from the neural axis caudal to the fifth somite (Le Douarin and Teillet, 1973). In rats, thoracic neural crest-derived cells were proposed to give rise to the superior cervical ganglion (SCG) (Rubin, 1985), but a later DiI labelling study in embryonic mice showed that NCC that emigrate from the neural tube adjacent to somites 1–4 (anterior vagal) also contribute to the SCG (Durbec et al., 1996). Since the seminal study by Le Douarin and Teillet (1973), many subsequent studies in avians, laboratory mammals and the Mexican axolotl (*Ambystoma mexicanum*) have confirmed that

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trunk NCC are the origin of paravertebral sympathetic ganglia (Lallier and Bronner-Fraser, 1988; Serbedzija et al., 1989, 1990; 1994; Epperlein and Lofberg, 1993; Epperlein et al., 1996; Kasemeier-Kulesa et al., 2005).

### 2.2. Migration

#### 2.2.1. Pathways of trunk NCC

In both mice and chicks, trunk NCC destined to form dorsal root and sympathetic ganglia migrate along a ventromedial route between the somites, and through the rostral half of each somite (Rickmann et al., 1985; Krull, 2001). Melanocyte precursors migrate along a dorsolateral pathway underneath the ectoderm. In most species, the first trunk NCC migrate ventromedially and later emigrating cells migrate dorsolaterally (Rickmann et al., 1985; Bronner-Fraser, 1986; Teillet et al., 1987; Serbedzija et al., 1989; Erickson et al., 1992; Anderson, 2000; Wilson et al., 2004). In contrast to other anamniotes and amniotes, in the axolotl, the migration of melanocyte precursors along the dorsolateral pathway occurs before the migration of NCC ventromedially (Epperlein et al., 2007).

Unlike mice and chicks where NCC migrate through the rostral half of each somite, NCC migrating along the ventromedial pathway in zebrafish embryos are found in both the rostral and caudal somite halves, but when they reach the level of the notochord, the cells converge between the segmental boundaries (Raible et al., 1992). In *Xenopus*, NCC in the ventromedial pathway migrate through the caudal regions of each somite (Krotoski et al., 1988; Collazo et al., 1993). In the axolotl, trunk NCC appear to migrate predominantly between the neural tube and the somites (Vogel and Model, 1977; Epperlein et al., 2007), although some migration through the somitic mesoderm has also been reported (Vogel and Model, 1977).

#### 2.2.2. Mode of migration

The migration of sympathetic neuron precursors has been reviewed recently (Kulesa et al., 2009). Time-lapse imaging studies in the chick have shown that, as they migrate ventrally, trunk NCC interact with their environment and neighbouring cells via extension and retraction of filopodia (Tosney, 1978; Kasemeier-Kulesa et al., 2005). Many of the cells migrate in chain-like formations (Kasemeier-Kulesa et al., 2005). In contrast, trunk NCC of urodeles appear to migrate as single cells (Epperlein et al., 1996). Kasemeier-Kulesa et al. (2005) also showed that some trunk neural crest-derived cells in the chick moved between sympathetic and dorsal root ganglia.

#### 2.2.3. Mechanisms controlling ventromedial migration of trunk NCC

In the chick embryo, ephrin-B ligands are expressed in the dorsolateral pathway coincident with ventromedial migration of NCC (Santiago and Erickson, 2002). Ephrin-B ligands appear to function first as repulsive guidance cues to repel early migrating NCC from the dorsolateral pathway, and they later stimulate the migration of melanocyte precursors dorsolaterally (Santiago and Erickson, 2002).

In chick and mouse embryos, the first NCC to emigrate along the ventromedial pathway migrate through the intersomitic boundary (Rickmann et al., 1985; Schwarz et al., 2009). The switch from an intersomitic to a sclerotome pathway is controlled by semaphorin 3A (Sema3A) and its receptor neuropilin-1 (Nrp1); *Sema3A* is expressed in the posterior sclerotome and the whole dermomyotome and acts as a repulsive cue to *Nrp1*-expressing trunk NCC (Schwarz et al., 2009). Other inhibitory molecules have also been implicated in restricting migration to the anterior somite in mouse and chick embryos, including Sema3F and its receptor neuropilin-2 (Gammill et al., 2006), Eph/ephrin signalling (Santiago and Erickson, 2002) and F-spondin (Debby-Brafman et al., 1999). In zebrafish, no Eph family members have yet been reported to be expressed in trunk NCC (Honjo and Eisen, 2005).

In mice, neuregulin (Nrg1) and its receptors, ErbB2 and ErbB3, are required for migration of trunk NCC ventrally to the dorsal aorta, where sympathetic ganglia form (Britsch et al., 1998). *ErbB3* expression is first detected in NCC as they emerge from the neural tube, while *Nrg1* expression is detected at the origin of NCC and along their migratory route. In *ErbB3*, *ErbB2* and *neuregulin-1* mutant mice, dorsal root ganglia form normally, but there is an accumulation of neural crest-derived cells dorsal to sites of sympathetic ganglion formation (Britsch et al., 1998). Britsch et al. (1998) proposed that Nrg1 does not act as a directional cue, but promotes motility of neural crest-derived cells destined to form sympathetic ganglia.

#### 2.2.4. Formation of sympathetic chain ganglia

Discrete sympathetic ganglia form as a consequence of significant reorganisation of NCC that initially coalesce adjacent to the dorsal aorta (Kasemeier-Kulesa et al., 2005). Although it had been assumed that segmental sympathetic ganglia form as a direct result of migration through the rostral half of each somite (Thiery et al., 1982; Lallier and Bronner-Fraser, 1988), more recently it has been demonstrated in mice, chick and zebrafish that NCC lose their segmental organization when they first arrive at the dorsal aorta, mix, and subsequently re-sort to form ganglia (An et al., 2002; Young et al., 2004a; Kasemeier-Kulesa et al., 2005, 2006). In avian embryos, individual sympathetic ganglia can be composed of cells that originate from up to six segments (Yip, 1986). The formation of sympathetic ganglia in the chick has been shown to involve integration of Eph/ephrin and N-cadherin-mediated interactions (Kasemeier-Kulesa et al., 2005, 2006). A correlation exists between the expression of *ephrin-B1* by the mesodermal tissue in the intersomitic regions and emigration of NCC away from the inter-ganglionic region to form ganglia (Kasemeier-Kulesa et al., 2006). Coupled with this, *N-cadherin*, expressed on post-migratory NCC (Hatta et al., 1987), promotes cell adhesion and ganglion formation (Kasemeier-Kulesa et al., 2006). Sema3A acting via Nrp1 receptors also appears to contribute to the aggregation of sympathetic precursors at the appropriate site (Kawasaki et al., 2002).

#### 2.2.5. Rostral migration to form the SCG

Precursors of the SCG reach their destination later than those of the thoracic ganglia (Rubin, 1985; Nishino et al., 1999). In mice, SCG precursor cells initially accumulate at the C1–C4 cervical vertebrae levels and form the rudimentary SCG between embryonic day (E) 11.5 and E14.5 (Nishino et al., 1999). The formation of the SCG is attributed to the rostral migration of precursor cells that originate from anterior vagal (Durbec et al., 1996) or lower cervical (Rubin, 1985) neural crest. Artemin, a member of the glial cell line-derived neurotrophic factor (GDNF) family that is expressed along blood vessels, is required for the rostral migration of SCG precursors, and their survival, in mice (Honma et al., 2002). Artemin signals through a multicomponent receptor consisting of Ret and GFRα3 (Baloh et al., 1998; Rosenthal, 1999; Airaksinen and Saarma, 2002). While most sympathetic ganglia of *Gfrα3*$^{-/-}$ mice appear normal, the SCG exhibit significant defects (Nishino et al., 1999). These defects result from failure of SCG precursors to migrate rostrally and, as a consequence, failure to innervate targets (Nishino et al., 1999). Failure to innervate target tissues leads to cell death of neurons in the SCG (Honma et al., 2002). The transcription factor, Phox2a, also appears to be involved in the rostral migration of SCG precursors (Section 2.4.1).

### 2.3. Proliferation

As in many parts of the nervous system (Edlund and Jessell, 1999), the proliferation of neurons and their precursors precedes that of glial cells in sympathetic ganglia of embryonic mice (CRA, unpublished). A striking feature of developing sympathetic ganglia in mammals, chicks, bullfrog and zebrafish is the division of cells expressing pan-