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DEVELOPMENT AT A GLANCE

The peripheral nervous system

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ABSTRACT

The peripheral nervous system (PNS) represents a highly heterogeneous entity with a broad range of functions, ranging from providing communication between the brain and the body to controlling development, stem cell niches and regenerative processes. According to the structure and function, the PNS can be subdivided into sensory, motor (i.e. the nerve fibers of motor neurons), autonomic and enteric domains. Different types of neurons correspond to these domains and recent progress in single-cell transcriptomics has enabled the discovery of new neuronal subtypes and improved the previous cell-type classifications. The developmental mechanisms generating the domains of the PNS reveal a range of embryonic strategies, including a variety of cell sources, such as migratory neural crest cells, placodal neurogenic cells and even recruited nerve-associated Schwann cell precursors. In this article, we discuss the diversity of roles played by the PNS in our body, as well as the origin, wiring and heterogeneity of every domain. We place a special focus on the most recent discoveries and concepts in PNS research, and provide an outlook of future perspectives and controversies in the field.

KEY WORDS: Schwann cell precursor, Nervous system development, Neural crest, Peripheral innervation, Peripheral nervous system, Placodes

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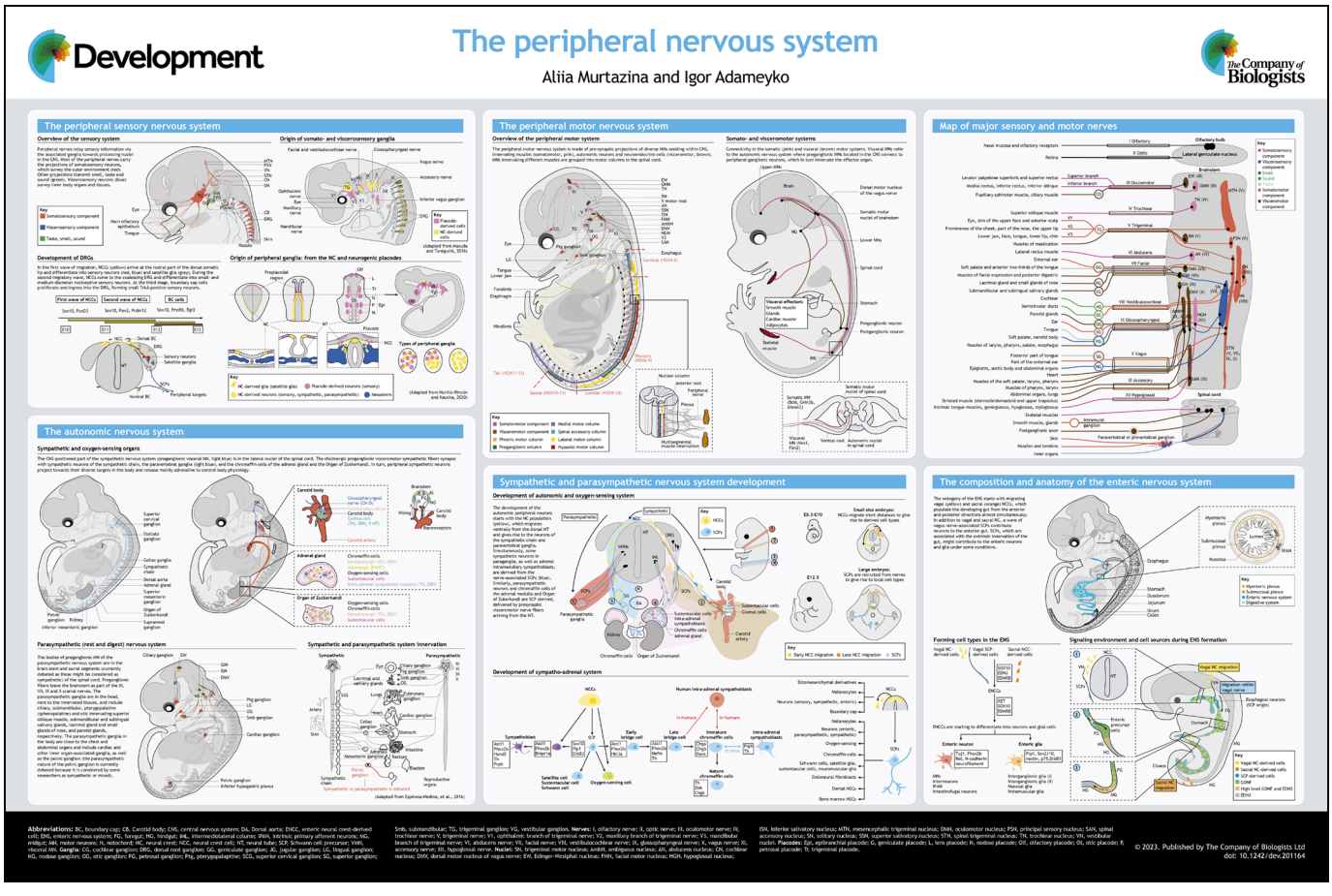
Introduction

The complexity of the nerves in the body is simultaneously tantalizing and elegant. For centuries, the innervation of the body was a hot topic of discussion among practicing surgeons, developmental biologists and classical neuroscientists alike (Hamburger and Levi-Montalcini, 1949; Horn, 2018; Rasulić,



Development (2023) 150, dev201164. doi:10.1242/dev.201164

2022). In recent years, the practical understanding of body innervation permitted the development of bionic interfaces and electroceuticals – technical solutions modulating or imitating activity of peripheral neurons for the benefit of patients (Adameyko, 2016; Russell et al., 2019; Shahriari et al., 2020).

Today, we know much more about the function, pathology, wiring and cell-type heterogeneity of the peripheral nervous system (PNS; see Table 1 for abbreviations). The PNS can be divided into three key domains: the sensory nervous system, which provides information about the environment (Le Pichon and Chesler, 2014); the motor system, which enables the voluntary and involuntary operation of our muscles and ensures the proper function of inner organs via the sympathetic and parasympathetic domains of the PNS (Stifani, 2014); and the autonomic nervous system, which can be further subdivided into sympathetic, parasympathetic and enteric (ENS) portions. The ENS provides sensory, information-processing and motor functions of the gut.

The PNS is crucial for development and homeostasis and, therefore, any significant abnormality of circuit formation, physiology and neuronal composition leads to pathologies, including a wide range of pain and other sensory- or motor-related problems (Lanigan et al., 2021), as well as the formation of PNS tumors, such as neurofibromatosis, schwannoma, neuroblastoma, pheochromocytoma and paraganglioma (Maguire et al., 2015). Here, we describe the structure and function of the PNS, including the sensory, motor and autonomic (including ENS), and briefly discuss the developmental origins of the cells that contribute to these systems.

Peripheral sensory nervous system

The sensory domain of the PNS includes several categories of neurons that allow us to obtain information from well-known senses, such as smell (olfactory system), sound (auditory system) and taste (gustatory system). At the same time, the majority of the peripheral nerves carry the projections of somatosensory neurons, which survey the body environment by collecting touch, pain (nociception), temperature (thermoception) and positional (proprioceptive) information. In addition, viscerosensory neurons survey the inner body tissues via nociception, mechanoreception, pressure (baroreception) and chemoreception (Schlosser, 2021; Vermeiren et al., 2020). Neurons in the PNS are organized into ganglia (structures containing many nerve-cell bodies) and the projections from these ganglia form peripheral nerves.

Table 1. List of abbreviations

Abbreviation	Term	Abbreviation	Term
BC	Boundary cap	III	Oculomotor nerve
CB	Carotid body	IV	Trochlear nerve
CNS	Central nervous system	V	Trigeminal nerve
DA	Dorsal aorta	V1	Ophthalmic branch of trigeminal nerve
ENCC	Enteric neural crest-derived cell	V2	Maxillary branch of trigeminal nerve
ENS	Enteric nervous system	V3	Mandibular branch of trigeminal nerve
IML	Intermediolateral column	VI	Abducens nerve
MNs	Motor neurons	VII	Facial nerve
N	Notochord	VIII	Vestibulocochlear nerve
NC	Neural crest	IX	Glossopharyngeal nerve
NCC	Neural crest cell	X	Vagus nerve
NT	Neural tube	XI	Accessory nerve
ORN	Olfactory receptor neuron	XII	Hypoglossal nerve
PNS	Peripheral nervous system	**Nuclei**	
PON	Primary olfactory neuron	5N	Trigeminal motor nucleus
SCP	Schwann cell precursor	AmbN	Nucleus ambiguous
SON	Secondary olfactory neuron	AN	Abducens nucleus
Ganglia		CN	Cochlear nucleus
CG	Cochlear ganglion	DMV	Dorsal motor nucleus of vagus nerve
DRG	Dorsal root ganglion	EW	Edinger-Westphal nucleus
GG	Geniculate ganglion	FMN	Facial motor nucleus
IVG	Inferior vagus ganglion	HGN	Hypoglossal nucleus
JG	Jugular ganglion	ISN	Inferior salivatory nucleus
LG	Lingual ganglion	MTN	Mesencephalic trigeminal nucleus
NG	Nodose ganglion	OMN	Oculomotor nucleus
OG	Otic ganglion	PSN	Principal sensory nucleus
PG	Petrosal ganglion	SAN	Spinal accessory nucleus
SG	Superior ganglion	SN	Solitary nucleus
TG	Trigeminal ganglion	SSN	Superior salivatory nucleus
VG	Vestibular ganglion	STN	Spinal trigeminal nucleus
Motor columns		TN	Trochlear nucleus
HMC	Hypaxial motor column	VN	Vestibular nuclei
LMC	Lateral motor column	**Placodes**	
MMC	Medial motor column	Epi	Epibranchial placode
PGC	Preganglionic motor column	L	Lens placode
PMC	Phrenic motor column	N	Nodose placode
SAC	Spinal accessory motor column	Ot	Otic placode
Nerves		P	Petrosal placode
I	Olfactory nerve	Tr	Trigeminal placode
II	Optic nerve		

Development (2023) 150, dev201164. doi:10.1242/dev.201164

The olfactory, auditory and gustatory systems

Olfactory information is received by nasal olfactory receptor neurons (ORN) collectively expressing a wide variety of receptors binding a spectrum of odorant molecules (Dang et al., 2018). ORN are primary sensory cells, and transmit information about sensory stimuli further into the olfactory bulb of the brain, where ORN synapse with mitral cells residing in glomeruli (Nagayama et al., 2014). Although ORN originate from a neurogenic placode, olfactory ensheathing glial cells are neural crest (NC)-derived (Barraud et al., 2010).

The auditory and vestibular stimuli are detected by hair cells in the Organ of Corti and vestibular structures. These are transmitted from the hair cells to the brain via secondary, placode-derived bipolar neurons residing in cochlear ganglion (CG) and vestibular ganglion (VG) (Delacroix and Malgrange, 2015; Highstein and Holstein, 2012).

Gustatory information is detected by primary sensory cells in the taste buds and is relayed by at least three types of secondary neurons. These include geniculate ganglion (GG) neurons, which transmit the signals from the taste buds of the anterior two-thirds of the tongue, neurons of the petrosal ganglion (PG), which innervate taste buds in the posterior third of the tongue, and nodose ganglion (NG) neurons that innervate the taste buds of the epiglottis (Lee et al., 2017).

Somatosensory system

Somatosensory neurons relay information from the skin, viscera and muscles (with tendons) about pain, temperature, touch and the position of body parts in space. They are predominantly organized into dorsal root ganglia (DRG), which are located adjacent to the length of the spinal cord. The sensory neurons of DRG are pseudo-unipolar and project to their peripheral targets, as well as to the spinal cord laminas, where they synapse specific populations of central nervous system (CNS) interneurons depending on their sensory modality. Major somatosensory modalities such as nociception (pain and temperature), mechanoreception (touch) and proprioception (position of body parts in space) are encoded in neurons via unique transcriptional profiles (and corresponding unique molecular characteristics, including ion channels) driven by specific transcription factor codes (Lallemend and Ernfors, 2012). Recent single-cell studies suggested updated classifications of somatosensory neurons (Kupari et al., 2021; Usoskin et al., 2015; Wu et al., 2021; Zeisel et al., 2018; Sharma et al., 2020) (Table 2), in agreement with lineage-tracing experiments, as well as morphological, electrophysiological, target tissue-related and other molecular studies (Lallemend and Ernfors, 2012; Zheng et al., 2019). Still, integration of different single-cell transcriptomics-based classifications of sensory neurons and their fine subtypes from several independent studies requires an additional future effort. Also, we still lack the full picture of how some fine sensory modalities are encoded, such as sensitivity to vibration or continuous pressure (Usoskin et al., 2010).

In addition to NC-derived DRG neurons, some somatosensory neuronal populations of the placode-derived trigeminal ganglion (TG), jugular ganglion (JG) and GG collectively innervate the head and neck tissues, together with primary proprioceptive neurons of mesencephalic trigeminal nucleus (MTN) located in the midbrain. The MTN somatosensory neurons are responsible for unconscious proprioception of the muscle spindles from the masticating muscles in the head and neck (Schlosser, 2021; Vermeiren et al., 2020).

Viscerosensory system

Viscerosensory neurons are responsible for sensing and transmitting information from internal organs, vessels and glands to the CNS. Some viscerosensory neurons are located in the DRG and project to inner organs (Smith-Anttila et al., 2020). The other viscerosensory neurons are located in the GG, such as the sensory ganglion of the facial nerve that innervates the nasal cavity, part of the palate and the sinus cavities.

The PG, also known as the inferior ganglion of the glossopharyngeal nerve, innervates the carotid body and provides sensory information from the tongue and pharynx areas. The NG, also known as the inferior ganglion of the vagus nerve, innervates receptors in the aortic bodies and aortic arch, and receives sensory signals from the heart, respiratory and gastrointestinal systems, and other inner tissues and organs, including the urinary tract (Schlosser, 2021; Vermeiren et al., 2020).

Recently, Kupari and colleagues took advantage of single-cell transcriptomics and characterized the viscerosensory neurons from JG and NG. They showed that the NC-derived neurons in JG are fundamentally similar to NC-derived somatosensory neurons in DRGs, including low threshold C-mechanoreceptors (C-LTMRs), A-LTMRs, Ad-nociceptors and C-nociceptors for cold and heat, and mechano-heat. Contrary to this, in the population of placode-derived neurons of NG, the authors identified 18 different types of viscerosensory neurons that did not appear to be related to or similar to somatosensory neurons in DRGs (Kupari et al., 2019).

Origins and development of the sensory system

Sensory neurons have two distinct origins during embryonic development: neurogenic placodes and the NC (Schlosser, 2021; Tolman et al., 2022). The mechanisms of emergence of the NC and placodes have been a hot topic throughout recent years, with different models of specification being discussed, including the ‘binary competence’ model, the ‘neural plate state’ model and the ‘gradient border’ model (Conti and Harschnitz, 2022; Thiery et al., 2022). Although the majority of the NC originates from the neural plate border, sacral NC might arise from neuromesodermal progenitors, with a possible brief phase of neuroectoderm as an intermediate (Lukoseviciute et al., 2021 preprint; Shaker et al., 2021). Furthermore, the recent successes in single-cell atlases have helped to delineate the hierarchy of transcriptional states and, to some extent, the downstream fate choices in the NC, based on co-activation of antagonistic fating programs before the point of commitment (Kastriti et al., 2022; Soldatov et al., 2019). The atlases of placodal development clarifying specification of downstream neuronal fates are still waiting to be generated and published.

Neurogenic placodes provide a major portion of sensory neurons emerging within olfactory, cochlear, vestibular, geniculate, trigeminal (partly), nodose and petrosal placodes. All neurogenic placodes originate from a putative horseshoe-shaped preplacodal ectoderm, found at the anterior edge of the neural plate, which subsequently breaks down into discrete placodal territories. Neuroblasts delaminate from the placodal neuroectoderm and ingress into underlying mesenchyme to form ganglia (Schlosser, 2021).

NC cells (NCCs) also contribute sensory neurons to a large part of TG, the entire JG and DRG (Schlosser, 2021). NCCs delaminate from the closing dorsal neural tube, migrate to specific destinations and undergo neurogenesis to form stereotypically positioned ganglia, sometimes via the intermediate stage represented by boundary cap (BC) stem cells (Hjerling-Leffler et al., 2005). Three waves of neurogenesis (from early NCC migration, from post-migratory proliferating progenitors and from BC cells) sequentially shape populations of DRG neurons, which acquire sensory specialization via segregation of expression of RUNX1 and RUNX3 transcription factors. Innervation of specific peripheral targets depending on

Development (2023) 150, dev201164. doi:10.1242/dev.201164

Table 2. Neuronal subtypes in different domains of PNS according to single cell studies and other experimental approaches

Neuron	Stage	Cluster	Subcluster	Gene expression	Reference
Dorsal root ganglia	Nociception				
	P30 (Usoskin et al., 2015)	Non-peptidergic	1	*Mrgprd*, *Prkcq*, *Agtr1a*	Usoskin et al., 2015
	P12-P30 (Zeisel et al., 2018)		2	*Calca*, *MrgprA3*, *Gfra1*, *Mlc1*	Zeisel et al., 2018
	Adult (Sharma et al., 2020)		3	*Tac1*, *Nppb*, *Nts*	Sharma et al., 2020
		Peptidergic	1	*Calca*, *Ntrk1*	
			2	*Calca*, *Tac1*	
			3	*Trpm8*, *Tac1*	
		TH-cluster	N.A.	*TH*, *Vglut3*, *Piezo2*	
	Mechanoreception				
	P30 (Usoskin et al., 2015)	Aβ RA-LTMR	N.A.	*Nefh*, *Ntrk2^{low}*, *Ret*, *Calb1*	Usoskin et al., 2015
	P12-P30 (Zeisel et al., 2018)	Aδ-LTMR	N.A.	*Nefh*, *Necab2*, *Cacna1h*	Zeisel et al., 2018
	Adult (Sharma et al., 2020)	Aβ Field -LTMR	N.A.	*Nefh*, *Fam19a1 (Tafa1)*, *Ret*	Sharma et al., 2020
	Proprioception (muscle afferents)				
	P56	Ia	CI.1	*Lmcd1*, *Runx1*	Wu et al., 2021
			CI.2	*Lmcd1*, *Calb1*	
			CI.3	*Lmcd1*, *Calb1/2*	
		II	CI.5	*Fxyd7*, *Cartpt*	
			CI.6	*Fxyd7*, *Tox*	
			CI.7	*Fxyd7*, *Aldh1a3*	
			CI.8	*Fxyd7*, *Chodl*	
		Ib	CI.4	*Chad*, *Pou4f3*	
Sympathetic neurons	P12-P30	Acetylcholine	SYCHO1	*Gal*, *Cartpt*, *Nog*, *Htr3a*, *Ly6e*, *Ccne1*, *Hctr1 (Hcrtr1)*, *Brip1*, *Cyp2j12*, *Ctla2a*, *Vip*, *Slc18a3*, *Pkib*	Zeisel et al., 2018
			SYCHO2	*Gal*, *Cartpt*, *Htr3a*, *Hctr1*, *Vip*, *Slc18a3*, *Gda*, *Pkib*, *Cadps2*	
		Noradrenaline	SYNOR1	*Gal*, *Htr3a*, *Brip1*, *Ccn1*, *Hcrtr1*, *Pkib*	
			SYNOR2	*Gal*, *Htr3a*, *Nog*, *Brip1*, *Ccne1*, *Hcrtr1*, *Pthlh*, *Gda*, *Pkib*	
			SYNOR3	*Gal*, *Htr3a*, *Ccne1*, *Hcrtr1*, *Cyp2j12*, *Pthlh*, *Gda*, *Pkib*	
			SYNOR4	*Gal*, *Htr3a*, *Ccne1*, *Hcrtr1*, *Cyp2j12*, *Ltk*, *Gda*, *Pkip*	
			SYNOR5	*Gal*, *Hcrtr1*, *Cyp2j12*, *Pthlh*, *Ltk*, *Gda*, *Pkip*	
Thoracic sympathetic ganglia	Adult	Noradrenaline	NA1	*Th*, *Dbh*, *Rarres1*	Furlan et al., 2016
			NA2	*Th*, *Dbh*, *Npy*, *Htr3a*	
			NA3	*Th*, *Dbh*, *Npy*	
			NA4	*Th*, *Dbh*, *Enc1*	
			NA5	*Th*, *Dbh*	
		Acetylcholine	ACh1	*Slc18a3*, *Vip*	
			ACh2	*Slc18a3*, *Vip*, *Sst*	
Enteric neurons (duodenum, jejunum, ileum)	P26	Motor neurons (excitatory)	ENC1	*Calb2*, *Ndufa4l2*	Morarach et al., 2021
			ENC2	*Calb2*, *Gda/Penk*, *Ndufa4l2*	
			ENC3	*Calb2*, *Gda/Penk*, *Ndufa4l2*	
			ENC4	*Fut9*, *Gda/Penk*, *Calb2*	
		Motor neurons (inhibitory)	ENC8	*Nos1*, *Npy*, *Rprml*	
			ENC9	*Nos1*, *Npy*, *Rprml*	
		Interneurons	ENC10	*Gad2*, *Nuerod6*, *Rprml*	
			ENC5	*Sst*, *Calb2*, *Calcb*	
		IPANS/ Interneurons	ENC6	*Nmu*, *Calb2*, *Calcb*	
			ENC7	*Ucn3*, *Cck*, *vGlut2 (Slc17a6)*	
			ENC12	*Nxph2*, *Ntng1*, *Calb1*, *vGlut2*	
		Uncategorized cluster	ENC11	*Npy*, *Th*, *Dbh*, *Calb2*	
Small intestine	P12-P30	Nitric oxide (Nos1)	ENT1, ENT2, ENT3	*Nos1*, *Slc5a7*, *Slc17a6*	Zeisel et al., 2018
		Cholinergic	ENT4, ENT5, ENT6, ENT9	*Chat*, *Slc5a7*	
			ENT7, ENT8	*Slc17a6*	

Continued

Development (2023) 150, dev201164. doi:10.1242/dev.201164

Table 2. Continued

Neuron	Stage	Cluster	Subcluster	Gene expression	Reference
Motor neurons	E9.5-E10.5	N.A.	MN.1	*Cldn3*, *Pou2f2*	Delile et al., 2019
	E9.5-E10.5	N.A.	MN.2	*Neurog2*, *Neurod2*, *Neurod4*	
	E10.5-E11.5	N.A.	MN.3	*Hes5*, *Olig2*, *Sox2*, *Sox9*	
	E11.5-E12.5	N.A.	MN.4	*Alcam*, *Casz1*, *Maf*, *Mecom*, *Pou3f1*, *Rxrg*	
	E12	N.A.	MN.5	N.A.	
	E10.5-E11.5	N.A.	MN.6	*Aldh1a2*, *Hoxc4*, *Hoxc5*	
	E10.5-E11.5	N.A.	MN.7	*Id2*, *Jun*, *Foxp1*, *Dab1*, *Mafb*	

E, embryonic day; N.A., not applicable; P, postnatal day.

neuronal subtype, as well as neuronal survival, are controlled by receptor tyrosine kinases NTRK1, NTRK2 and NTRK3 and cognate ligands. When it comes to projecting into the CNS, SEMA3A sets up modality-specific targeting of interneurons in the spinal cord (Marmigère and Ernfors, 2007).

Quite remarkably, one of the studies highlights that, although the vast majority of neurons in CG and VG originate from otic placodes, NCCs might potentially also contribute a minor proportion of neurons (D'amico-Martel and Noden, 1983). At the same time, the glial component of all peripheral ganglia (including of placodal origin) is NC-derived. The spectrum of physiological roles of satellite glial cells and embryonic Schwann cells remains not fully understood, although there is a clear dependency of mature sensory neurons on the glial compartment (Avraham et al., 2022). Strikingly, there is a population of nociceptive Schwann cells in the skin that responds to pain stimuli and assists the pain reception of associated nociceptive nerve fibers (Abdo et al., 2019; Rinwa et al., 2021).

Unlike other sensory neurons from the peripheral ganglia, the MTN is located inside of the CNS and originates from embryonic progenitors, the nature of which is not known, and is assumed to be either of NC or CNS radial glial progenitor origin. However, experiments have shown the absence of NC markers in MTN progenitor cells (Hunter et al., 2001).

Peripheral motor nervous system

The peripheral motor nervous system is made of projections of diverse CNS-positioned motor neurons (MNs) innervating muscles and synapsing with autonomic neurons and neuroendocrine cells that control the inner organs.

Cranial MNs

The branchial and somatic MNs residing in the brain project to the periphery with the outgoing cranial nerves. These nerves include the oculomotor nerve (III; oculomotor nucleus, eyeball movements), the trochlear nerve (IV; trochlear nucleus, controls the contralateral superior oblique eye muscles), the mandibular branch of the trigeminal nerve (V3; trigeminal motor nucleus, controls muscles of mastication), the abducens nerve (VI; abducens nucleus, controls the ipsilateral and lateral rectus muscle), the facial nerve (VII; facial nucleus, facial movements and expressions), the glossopharyngeal nerve [IX; inferior salivary nucleus (ISN), stylopharyngeus muscle responsible for elevating the larynx and pharynx, especially during speaking and swallowing], the vagus nerve [X; nucleus ambiguous (AmbN), sends branchiomotor fibers controlling swallowing and speaking], the spinal accessory nerve (XI; spinal accessory nucleus, controls sternocleidomastoid muscle) and the hypoglossal nerve (XII; hypoglossal nucleus, controls muscles of the tongue including the intrinsic muscles and also the geniohyoid muscle) (Jacobson and Marcus, 2008).

Somatic motor neurons in brain nuclei are divided into three groups: alpha neurons innervate extrafusal muscle fibers (slow-twitch fatigue-resistant, fast-twitch fatigue-resistant, fast-twitch fatigable), beta neurons innervate both intrafusal (static fibers, nuclear chain fibers and dynamic fibers, the nuclear bag fibers of muscle spindles) and extrafusal muscle fibers, and gamma neurons, which exclusively control the sensitivity of muscle spindles (Shneider et al., 2009; Stifani, 2014).

Spinal MNs

The spinal somatic MNs innervate skeletal muscles and are organized into distinct anatomical columns extending along the rostro-caudal axis. These columns include the medial motor column (MMC) innervating axial musculature, the lateral motor column (LMC) innervating the limbs, the hypaxial motor column (HMC) innervating the body wall and intercostal muscles, the preganglionic column (PGC) innervating the sympathetic chain ganglia and chromaffin cells of the adrenal gland, the spinal accessory column (SAC) innervating mastoid muscles as well as four muscles of the neck, and phrenic motor columns (PMC) innervating the diaphragm (Jacobson and Marcus, 2008; Tsuchida et al., 1994).

Visceral MNs

Visceral preganglionic MNs specifically express the master transcriptional factor, Phox2b, in an evolutionarily conserved manner (Nomaksteinsky et al., 2013) and control the operation of peripheral autonomic neurons and neuroendocrine cells via cholinergic neurotransmission (Stifani, 2014). The visceral preganglionic MNs of the sympathetic system form the intermediolateral column (IML) of the spinal cord. They innervate paravertebral and prevertebral sympathetic ganglia chains, as well as chromaffin cells of adrenal medullae and the Organ of Zuckerkandl. Recently, single-cell studies have helped to characterize 16 clusters of sympathetic visceral MNs in an adult mouse (Table 2) (Blum et al., 2021). The preganglionic MNs of the parasympathetic system are located in the Edinger-Westphal nucleus EW; and other nuclei) and project via cranial nerves III, VII, IX and X towards parasympathetic ganglia (Purves, 2001). The former sacral subdivision of the parasympathetic nervous system could now be considered sympathetic based on the fact that the corresponding preganglionic neurons express Olig2 and Foxp1, a specific combination for sympathetic preganglionic visceral MNs (Espinosa-Medina et al., 2016).

The use of sympathetic or parasympathetic terminology in relation to sacral autonomic domain is still debated in the field, as extensively summarized in Horn (2018). Some researchers support the view that parasympathetic and sympathetic domains are defined via their roles in the body and are not based on transcription factor expression, whereas other experts suggest that neuronal identity and specifics of wiring play a leading role (Espinosa-Medina et al., 2016; Horn, 2018).

Development (2023) 150, dev201164. doi:10.1242/dev.201164

Some motor fibers travel with the vagus nerve and control the motility of the gut (see ENS section below) and arrive from the dorsal motor nucleus and the AmbN in the CNS.

Origin and development of the peripheral motor nervous system

During embryonic development, somatic brainstem and spinal MNs originate from the radial glia progenitor cells located along the dorsoventral axis of the neural tube. They arise from the pMN domain expressing the transcription factor, Olig2 (Takebayashi et al., 2000). Different factors generate a gradient along the rostral-caudal axis, which promotes graded expression of various proteins of the Hox family of transcription factors, which drive the acquisition of different MN cell identities associated with anatomically distinct motor columns (Bel-Vialar et al., 2002; Dasen et al., 2003; Ensini et al., 1998). In contrast to somatic columnar MNs, branchial MNs of the brainstem arise from the ventral-most p3 domain that expresses Nkx2.2 and Nkx2.9 (Holz et al., 2010). Recently, single-cell studies have helped to clarify the development of spinal MNs and revealed embryonic MN-related clusters (Delile et al., 2019), as well the diversity of adult MNs (Alkaslasi et al., 2021; Blum et al., 2021) (Table 2).

The autonomic nervous system

Traditionally, the autonomic nervous system is divided into parasympathetic (rest and digest) and sympathetic (fight or flight response) branches, which are primarily defined by their largely antagonistic functions. Often, ENS is also included into the autonomic nervous system domain.

Parasympathetic

In the parasympathetic system, CNS-located visceromotor neurons project with long cholinergic fibers that navigate to distantly developing parasympathetic ganglia, close to the organs they innervate. Then, parasympathetic neurons make shorter, largely cholinergic, projections towards glands and other target tissues (Espinosa-Medina et al., 2016). The exact diversity of parasympathetic neurons is currently unknown, although most of them are cholinergic.

Sympathetic

Visceromotor neurons in the neural tube produce relatively short cholinergic axons targeting stereotypically positioned sympathetic ganglia. In turn, sympathetic ganglia produce longer, mostly adrenergic, axons to target blood vessels, glands and other tissues they control. The sympathetic branch includes sympathetic neurons with associated glial cells, as well as neuroendocrine chromaffin cells.

Chromaffin cells of the adrenal gland and the transient Organ of Zuckerkandl include adrenergic (only in adrenal glands) and noradrenergic neuroendocrine cell populations producing and releasing hormones into the blood flow. Recently, the existence of an additional human-specific chromaffin progenitor population has been suggested based on the expression of nicotinic acetylcholine receptor (AChR); however, there is currently no evidence that this population expresses cholinergic genes, such as choline acetyltransferase (*CHAT*) and vesicular acetylcholine transporter (*VACHT*; also known as *SLC18A3*) (Bedoya-Reina et al., 2021).

Single-cell transcriptomics and tissue-based analysis of sympathetic neuron diversity has revealed the existence of eight neuronal cell types in the sympathetic nervous system: five types of adrenergic neurons, two types of cholinergic neurons and one glutamatergic neuronal subtype (Table 2) (Furlan et al., 2016). The most recent analysis of developmental strategies, wiring and transcriptional factor expression has suggested that the sacral domain of the parasympathetic nervous system should be reassigned to be sympathetic (Espinosa-Medina et al., 2016). These recent changes in nomenclature and developmental paradigm have caused intense discussions and friction in the community (Hoehmann and Cuoco, 2017; Jänig and Neuhuber, 2017; Jänig et al., 2018).

Oxygen-sensing organs

A part of the sympathetic system is dedicated to oxygen sensing: chromaffin cells and the cells of the carotid oxygen-sensing organ are involved in a hypoxia-sensing pathway and express oxygen sensing-related gene *Epas1*, *Cox4i2* and *Olfr78* (*Or51e2*). Chromaffin cells respond to hypoxia by releasing catecholamines that influence the breathing pattern, whereas the serotonergic cells of the carotid organ signal onto the afferent branches of the glossopharyngeal nerve to elicit a CNS-mediated response to hypoxia (Hockman et al., 2018; López-Barneo et al., 2016).

Origin of the autonomic nervous system

The development of all postganglionic autonomic peripheral neurons starts with the NC population, which migrates ventrally from the dorsal neural tube and gives rise to the neurons of the sympathetic chain and large proportion of paravertebral ganglia. The ventral migration and autonomic priming of NCCs is supported by BMPs and SDF1 (CXCL12) generated by cells near the dorsal aorta (Saito and Takahashi, 2015). At the same time, some sympathetic neurons in paraganglia and intramedullary sympathoblasts are immediately derived from nerve-associated Schwann cell precursors (SCPs), multipotent progenitors originating from the NC that settle on the nerves (Furlan and Adameyko, 2018; Kameneva et al., 2021a,b; Kastriti et al., 2019). Via a similar mechanism, parasympathetic neurons and chromaffin cells of the adrenal medulla and the Organ of Zuckerkandl originate from SCPs delivered by presynaptic fibers arriving from the neural tube (Dyachuk et al., 2014; Espinosa-Medina et al., 2014; Furlan et al., 2017). The local paracrine, placental and systemic maternal serotonin influences the process of transition from SCP into chromaffin cell, thus limiting the size of the adrenal medulla (Kameneva et al., 2022). SCPs also give rise to other cell fates including melanocytes, enteric neurons and even some skeletogenic and odontogenic mesenchymal cells (Furlan and Adameyko, 2018; Xie et al., 2019), which signifies the role of the PNS and nerve-associated SCPs in the development of other tissues and organs in the body.

Enteric nervous system

The ENS controls motility of the gut and, in addition, performs a number of roles connected to interaction with the microbiome, brain and immune system (Geng et al., 2022; Spencer and Hu, 2020). The diversity of neuronal subtypes in the ENS is astonishing, as they are performing different roles in a connectome, including sensory, motor and interneuron functions (Lasrado et al., 2017; May-Zhang et al., 2021; Morarach et al., 2021; Obata et al., 2022). The number of neurons in the ENS is close to the number of neurons in the spinal cord, although the reasons for this number of neurons are unknown. Most enteric neurons are organized into ganglia that are positioned in different layers of the gastrointestinal system. The most recent classifications based on single-cell transcriptomics in mice and humans suggest that there are 12-14 types of enteric neurons with different transcriptional programs, positions, functions and neurotransmitter specificity (Table 2) (Lasrado et al., 2017; May-Zhang et al., 2021; Morarach et al., 2021). The anterior-posterior

Development (2023) 150, dev201164. doi:10.1242/dev.201164

diversity of neuronal populations along the length of the ENS and its different parts such as the esophagus, stomach, duodenum etc. is poorly studied, although there is some progress in this direction (May-Zhang et al., 2021). The ENS connects to the CNS via the vagus nerve, which carries both afferent and efferent fibers. This connection is receiving increased attention ever since the discovery of a gut-brain axis (Breit et al., 2018). Beyond controlling gut motility, neuronal cells of the gut interact with immune cells and the microbiome (Fried et al., 2021). Similarly, glial cells of the ENS also perform several other functions, including immune interactions during parasitic invasion (Progatzky et al., 2021).

Origin and development of the enteric nervous system

The ontogeny of the ENS starts with migrating vagal and sacral NCCs, which populate the developing gut from the anterior and posterior directions almost concurrently (Nagy and Goldstein, 2017). The vagal NC ingresses along the fibers of the outgrowing vagus nerve, and specific signaling cascades ensure propagation of the enteric NC inside of the gut. The key signaling molecules regulating colonization of the gut by enteric crest include GDNF, EDN3, RET, and EDNRB (Lake and Heuckeroth, 2013). Some NCC-derived progenitors migrate into the intestine via the mesentery (Nishiyama et al., 2012). This question of the exact nature of mesenteric and trans-mesenteric NC is still open to debate and further study, and is discussed by Yu et al. (2021).

Problems with enteric NC or these signals often result in an aganglionic gut (Hirschsprung's disease) (Rao and Gershon, 2018). In addition to vagal and sacral NC migratory streams, a wave of vagus nerve-associated SCPs contributes neurons to the anterior gut (Espinosa-Medina et al., 2017). At the same time, SCPs associated with extrinsic innervation might also be recruited into the gut under some conditions (Laranjeira et al., 2011). This is a promising therapeutic strategy for populating aganglionic regions of the gut with new neurons. For more information on the development of the ENS, we refer the reader to Kang et al. (2021).

Concluding remarks

The recent technological revolution related to single-cell multi-omics approaches resulted in an unbiased and systematic way of looking at the cell populations building different parts of the PNS in the postnatal body and during embryonic development (Kameneva and Adameyko, 2019). Applications of single-cell transcriptomics and epigenomics have not only revealed novel embryonic progenitors and mature neuronal subtypes, but also provided a wealth of data about the differentiation trajectories and fate selection at different developmental stages (Kastriti et al., 2022).

However, our knowledge of the diversity of cell types in some parts of the PNS is still lagging behind, which is the case for the parasympathetic domain due to poor accessibility of corresponding ganglia. Therefore, the single-cell atlases of parasympathetic neurons and glial cells are yet to come. In the ENS, the information-processing and wiring logic are poorly understood due to the absence of known standard circuitry units, although the single-cell atlases are in place. In the case of the somatosensory sub-system, we still do not understand how the finest sensory modalities (vibration, permanent pressure) are genetically encoded, and if there are corresponding neuronal subtypes with their own molecular identity codes (Usoskin et al., 2010). In addition, we do not understand how those modalities are wired into the brain. Also, the itch (pruriception) pathway remains elusive (Chen and Sun, 2020; Davidson and Giesler, 2010). Finally, although a wealth of knowledge about the roles, neuroanatomy, composition and ontogeny of the PNS has been generated over last century, how the different parts of the PNS coordinate during wiring and activity remains a challenge. Eventually, further improvements of single-cell multi-omics approaches and atlases of the PNS, combined with viral tracing of connectivity, opto- and chemogenetics approaches, functional multiplexed experiments and spatial transcriptomics, will help to solve the remaining questions in the domain of PNS research.

Competing interests

The authors declare no competing or financial interests.

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High-resolution poster

A high-resolution version of the poster is available for downloading in the online version of this article at https://journals.biologists.com/dev/article-lookup/doi/10.1242/dev.201164#supplementary-data.

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