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Peripheral Somatosensation: A Touch of Genetics

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Summary

The somatosensory system processes information that organisms “feel”: joint position, muscle stretch, pain, pressure, temperature, and touch. The system is composed of a diverse array of peripheral nerve endings specialized to detect these sensory modalities. Several recent discoveries have shed light on the genetic pathways that control specification and differentiation of these neurons, how they accurately innervate their central and peripheral targets, and the molecules that enable them to detect mechanical stimuli. Here, we review the cadre of genes that control these processes, focusing on mechanosensitive neurons and support cells of the skin that mediate different aspects of the sense of touch.

Introduction

Five sensory systems (hearing, olfaction, somatosensation, taste and vision) provide organisms with environmental information critical to their survival. Each system detects specific types of stimuli and transmits this information to the brain, where it is processed and integrated into sensory percepts, or constructs of the world around us. Of the five, only the somatosensory system is multimodal, detecting different types of stimuli including joint position (proprioception), noxious stimuli, temperature, and touch. Touch itself can be further subdivided into detection of curvature, hardness, shape, texture, pruriception (itch detection), and pleasurable touch [1–3]. The ability to detect and discriminate between these widely varied stimuli is achieved in mammalian skin by multiple sensory receptors specialized to provide modality-specific communication to the central nervous system [4].

Cell bodies of sensory neurons that innervate the periphery are located predominantly in cranial and dorsal root ganglia (DRGs) next to the spinal cord. These neurons possess a single axon that bifurcates to send one process into the dorsal spinal cord and the other to the skin [5]. Mature mammalian DRGs contain a heterogeneous population of neurons specialized for detection of different somatosensory signals (TABLE 1) [1,2,6–10]. These cells can be classified on the basis of morphology, neurochemistry, and trophic requirements

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[5]. Here, we focus on recent developments that extend our knowledge of somatosensory mechanoreceptors.

Genetic Specification and Differentiation of Somatosensory Neurons

DRG neurons originate from neural crest cells (NCCs) that migrate ventrally from the dorsal neural tube during three distinct waves of migration (reviewed in [11]). Most adult DRG neurons derive from the second migratory wave, while NCCs in the first and third waves exhibit limited cell division [12,13]. Each wave of NCC migration and neurogenesis gives rise to unique populations of DRG neuron subtypes [13,14]. NCCs of the first wave give rise to large mechanoreceptive and proprioceptive neurons [12,15], those of the second wave produce all sensory neuron types [12], and the final wave gives rise to nociceptors and glia [13,16]. All NCC sensory neuron precursors express the transcriptional activator *Sox10* (*sex determining region Y box 10*) throughout migration and in the DRG [17], which maintains their multipotency [18]. NCCs of the third wave also express the transcription factor *Egr2* (*Krox20*) [13,16].

Following delamination from the neural tube, sequential expression of transcription factors specifies NCCs for different sensory neuronal fates (FIGURE 1). First, the proneural gene *Neurogenin 2* (*Ngn2*) is transiently expressed by migratory NCCs [14,19–21]. High levels of *Ngn2* expression in NCCs of the first migratory wave prompt rapid acquisition of sensory neuron fate, while later migrating NCCs have low or no *Ngn2* and remain uncommitted. NCCs of the second and third waves instead express *Ngn1* after arrival in the DRG [14,19–21]. Targeted deletion of *Ngn2* in mice causes relatively minor neuronal loss, presumably secondary to functional compensation by *Ngn1* [14]. Conversely, the majority of DRG neurons are missing in *Ngn1*-null mice, and no somatosensory neurons are formed in *Ngn1/Ngn2*-null mice [14]. Although the *Ngns* specify NCCs to the sensory lineage and their presence correlates with distinct waves of neurogenesis, they do not appear to specify sensory neuron subtypes [22].

Following *Ngn*-imposed commitment of NCCs to a neuronal fate, three other transcription factors are expressed by all somatosensory neurons. *Brn3A* is first expressed in migratory *Sox10*⁺/*Ngn2*⁺ NCCs [17], where it regulates the transition from neurogenesis to terminal differentiation and represses non-neural gene expression [23]. *Brn3A* is required for specification and survival of proprioceptive, mechanoreceptive, and nociceptive neuron subpopulations [24–26]. Next, *Foxs1* expression is initiated in migratory *Brn3A*⁺ cells that no longer express *Sox10* [17]. The precise role of this transcription factor is unclear, as deletion does not appear to affect neuronal production or function [27]. Finally, *Islet1* represses genes involved in neurogenesis and plays a central role in the transition to subtype specification. *Islet1* deletion in NCCs causes complete loss of cutaneous sensory fibers subserving pain, touch, and temperature, though proprioceptors are spared [28]. Together, these transcription factors set the stage for subsequent differentiation events.

The Roles of Neurotrophins

The neurotrophins (NTs) are a group of related molecules whose canonical role is to promote neuronal survival. NTs are expressed in sensory neuron target areas and mediate their effects through specific high-affinity receptors (NTRs) located on innervating axons. Each NT supports survival of different, sometimes overlapping, neuronal populations through restricted expression of NTRs. In adult mammalian DRGs, proprioceptors and slowly-adapting type I low-threshold mechanoreceptors (LTMRs) express TrkC (Ntrk3) [29–31]. Other LTMRs express TrkB (Ntrk2) and/or Ret and glia-derived neurotrophic factor (GDNF) [30,32–35]. Nociceptors, thermoceptors, pruriceptors, and C-mechanoreceptors express TrkA (Ntrk1) [36–39].

DRG neurons are initially generated in excess. As they innervate their targets, axons encounter limited amounts of growth factors and compete for survival. DRG neurons that compete successfully bind NTs or members of the GDNF family of ligands (GFLs) and retrogradely transport them to their cell bodies, inducing expression of anti-apoptotic and pro-survival genes (FIGURE 2) [40,41]. In the absence of NTs, NTRs such as TrkA and TrkC instruct neurons to die [42] and the corpses are removed by glial precursors [43]. Deletion of NTs or NTRs results in loss of the corresponding classes of neurons (TABLE 2) [29–39,44–65]. Interestingly, *BDNF*-, *NT3*-, and *TrkB*-null mice also lose DRG neurons prior to target innervation [59], suggesting that intrinsic NT signaling within the DRG plays a role prior to acquisition of target dependence.

The pro-apoptotic gene *Bax* is necessary to activate NT-mediated cell death pathways, and *Bax* deletion rescues all DRG neurons [66]. *Bax*-null mice exhibit cutaneous hyperinnervation and subsequent functional hypersensitivity. In contrast, proprioceptor numbers are normal secondary to limiting concentrations of muscle NT-3. These results suggest that cutaneous sensory neurons may be able to regulate NT production in an innervation-dependent manner [66].

NTs are also important for DRG neuron differentiation and identity maintenance. During early DRG development, all postmitotic neurons express the high affinity NT-3 receptor TrkC [67], which is downstream of Brn3A function [26]. TrkA is expressed next and partially overlaps with TrkC expression at these early developmental stages [28]. Refinement of widespread NTR expression into the distinct subpopulations seen in adult DRGs is associated with terminal differentiation of somatosensory neurons. TrkC+ neurons are biased towards LTMR and proprioceptor fates by expression of the transcription factor *Runx3* [68]. Proprioceptors segregate from LTMRs by maintained expression of *Runx3*, which suppresses *TrkB* expression and maintains *TrkC* expression [69,70], and by rapid down-regulation of *Islet1* [28]. Most mature LTMRs express TrkB, and their differentiation is controlled in part by GFLs. GFLs signal through receptor complexes containing the receptor tyrosine kinase Ret and a GPI-anchored ligand binding subunit GFL receptor (GFR). *Ret*+/*GFRa2*+ DRG neurons become rapidly-adapting LTMRs [32,34], and the transcription factor MafA interacts with Ret to promote their differentiation and diversification [32]. It is not clear whether slowly-adapting LTMRs are *Ret*-dependent [32,34], and the mechanisms that control their differentiation have not been established. NTs also function to maintain neuronal identity [37,71–73], although how this occurs is not understood.

Finally, NTs exert direct effects on neuronal function. Target-derived BDNF is necessary for mechanosensitivity of slowly-adapting LTMRs [48,74] and GDNF decreases C-fiber mechanical thresholds [75]. Both of these effects may in part be modulated by upregulation of the putative mechanosensitive ion channel ASIC2 (see below) in the DRG.

Sensory Neuron Projections

Proper targeting of sensory afferents requires coordinated neurite outgrowth, branching, and axon maintenance (reviewed in [76,77]). Several signaling pathways modulate these processes (FIGURE 2).

NTs stimulate neurite outgrowth through actions separable from those that promote neuronal survival. Deletion of *Bax* in *NGF*-, *TrkA*-, *NT3*-, and *Ret*-null mice rescues DRG neurons from apoptosis but alters central and peripheral projections [37,78,79]. These actions are modulated by Linx, a leucine-rich repeat and immunoglobulin family protein localized to the cell membrane [80], and by Mint2, which suppresses NGF-TrkA stimulated neurite outgrowth by binding TrkA [81]. Another neurotrophin, fibroblast growth factor (FGF),

stimulates axon elongation through Ras/Raf/ERK signaling [82]. This pathway is suppressed by Sprouty2, a molecule that limits the intensity and duration of tyrosine kinase activation [83]. These reciprocal interactions insure that elongation occurs without overgrowth.

Axon guidance and terminal branching are controlled by different environmental cues. Semaphorins (Sema), a family of secreted and transmembrane proteins expressed in tissues surrounding growing neurons, act as axon guidance molecules. Semaphorins signal through heterodimeric receptor complexes composed of transmembrane plexin (Plex) family members and neuropilin (Nrp) receptors expressed on neurons [84–87]. Disruption of Sema3A-Nrp1 signaling results in axon defasciculation and inhibits branching of peripheral sensory neuron projections [88,89]. Other proteins, such as the inhibitory growth protein NogoA, are expressed by glia as well as neurons. Neuronal Nogo-A controls peripheral axon fasciculation and stimulates branching through repulsive/anti-adhesive effects upon binding the Nogo receptor complex, promoting downstream Rho-ROCK activation [90]. Likewise, NT-NTR signaling stimulates axon branching balanced by intracellular cGMP inhibition generated by the GSK3 pathway [91]. Finally, pruning of branches occurs after establishment of primary target contacts and is regulated by the actions of the fusogen EEF1 [92] and adenylate cyclase 1 [93].

The Genetics of Mechanotransduction

Mouse LTMRs become mechanotransduction-competent coincident with peripheral target innervation at the astonishingly early age of E13 [94]. This ability is independent of NT3 activity but is consistent with changes in *Runx3* expression that likely occur prior to target innervation [51,95], suggesting that local determinants regulate *Runx3* expression and define many aspects of mechanoreceptive (and proprioceptive) phenotypes.

Elucidation of the processes by which mechanical stimuli are transformed into electrical responses in mammalian cutaneous mechanoreceptors has proven elusive. Most of what is known about mechanosensitive proteins comes from work in *Caenorhabditis elegans* and *Drosophila* (reviewed in [96]). Some of these proteins are ion channels linked to the extracellular matrix through a protein tether that may serve to direct force to the channel or to the immediate lipid environment surrounding the channel [97]. ASIC1 and ASIC2 (acid-sensing ion channels) are mammalian homologs of the *C. elegans* degenerin/epithelial Na⁺ channel (DEG/ENaC) that localize to discrete regions of Pacinian corpuscles, suggesting they may have specific roles in mechanotransduction [98]. Piezo1 and Piezo2 are multipass transmembrane proteins required for rapidly adapting, mechanically-activated cation channel activities in DRG neurons [99]. It is unclear whether Piezos are ion channels or non-conducting subunits of ion channels required for proper channel expression and/or modulation of channel properties. Recently, the zebrafish gene *touché* was shown to be required for generator potentials in response to light touch, though the identity of the protein and how it participates in conversion of tactile stimuli into electrical responses remains unknown [100].

Somatosensory Cells in the Skin

Merkel cells, a unique cell population found at the epidermal/dermal border, form complexes with slowly-adapting type I nerve fibers. Merkel cells are derived from the epidermal lineage [101,102] and express the transcription factor Atoh1, which is required for their production [103]. Similar to their innervating neurons, Merkel cells exhibit NT dependence and are lost in *BDNF*-, *NGF*-, *NT3*-, *p75*, *TrkA*-, *TrkB*-, and *TrkC*-null mice [29,35,36,55]. Conversely, over-expression of *NT3* and *BDNF* results in increased Merkel cell numbers [46,56,57]. These NT effects on Merkel cells appear to be secondary to effects on innervating nerve fibers [29,31,36,44,46,56]. Merkel cells have long been proposed to be

mechanotransducers. In support of this hypothesis, they make synaptic connections with sensory terminals, express synaptic machinery, and are essential for light touch responses [103–105]. However, how Merkel cells transduce mechanical signals remains unknown.

Other potentially mechanosensitive cells in the skin include keratinocytes and glia [96]. Within Pacinian corpuscles, modified Schwann cells of the capsule release GABA that inhibits glutamatergic excitation of the neuron during sustained pressure [106]. However, if and how these cells function in touch sensation is unknown.

Concluding Remarks

Genetic animal models have provided invaluable insights into the mechanisms underlying peripheral somatosensory system development. However, several key questions remain. What genetic pathways control terminal differentiation of LTMR subclasses? How are cutaneous mechanoreceptors targeted to specific skin regions? And, at the most basic level, how do peripheral mechanoreceptors work? Newly developed genetic tools, such as combinatorial fate mapping and channelrhodopsins, should provide tractable experimental avenues to address these issues.

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Figure 1.
Genetic cascades that control neurogenesis and subtype specification of low-threshold mechanoreceptors (LTMRs).

Figure 2.
Signaling pathways that modulate neurite outgrowth, branching, and neuronal survival.

Table 1

Mature mammalian DRG somatosensory neurons.

Afferent Fiber Type	Myelination	Soma Size	Modality	Associated Receptors	References
A α	Thick	Large	Proprioception	Muscle spindle	[6]
				Golgi tendon	
A β – rapidly adapting	Thick	Large	Low-threshold touch	Meissner corpuscle	[1]
				Pacinian corpuscle	
				Lanceolate endings	
A β – slowly adapting	Thick	Large	Low-threshold touch	Merkel cell/neurite complex	[1]
				Ruffini corpuscle	
A δ	Thin	Medium	Noception	Mechanoreceptor	[2,7,8,9]
				Polymodal	
			Thermoeception	Thermoeceptor	
				Mechanoreceptor	
			Pruriception	Polymodal	
C	None	Small	Noception	Mechanoreceptor	[2,7,8,9]
				Polymodal	
			Thermoeception	Thermoeceptor	
				Mechanoreceptor	
				Polymodal	
			Pruriception	Chemoceptor	
				Mechanoreceptor	
			Pleasant touch	Polymodal	[10]
				Mechanoreceptor	

Table 2

Effects of NTs and NTRs on somatosensory neurons. Innervation includes presence of axons, axon branching, and presence of Merkel cells. OE, overexpressor; ↓, decreased; ↑, increased; ↔, no change compared to wild-type

Model	All neurons	Aα	Aβ - RA	Aβ - SA	Aδ	C	Innervation	References
TrkA ^{-/-}	↓		↓	↓	↓	↓	↓	[29,36,37,38,39]
NGF ^{-/-}	↓		↓	↓		↓	↓	[36,37,49]
NGF OE	↑	↑	↑	↑	↑	↑		[47,61]
TrkB ^{-/-}	↓	↔	↓	↓/↑	↓	↔	↓	[30,35]
BDNF ^{-/-}	↓	↔	↓	↓/↑	↔	↓/↔		[36,48,50,54,58,59,65]
BDNF OE	↔	↑	↑	↑	↑		↑	[57]
NT4 ^{-/-}	↓	↑			↓	↔		[58,60,62,64]
TrkC ^{-/-}	↓	↓	↑	↓		↔	↓	[29,30,31]
NT3 ^{-/-}	↓	↓	↑	↓/↑	↓	↓	↓	[29,31,36,45,51,52]
NT3 ^{+/-}			↑	↓	↓		↓	[44]
NT3 OE	↑	↑	↑	↑	↑	↑	↑	[46,56]
p75 ^{-/-}	↓	↓	↔	↔; ↓	↓	↑/↓	↓	[36,55,63]
Ret ^{-/-}		↔	↓	↓/↔		↔/↓	↓	[32,34,53]
GDNF ^{+/-}			↓	↓;↔		↔	↓	[33]