Published in final edited form as:
Cell. 2011 July 8; 146(1): 178–178.e1. doi:10.1016/j.cell.2011.06.038.

SnapShot: Spinal Cord Development

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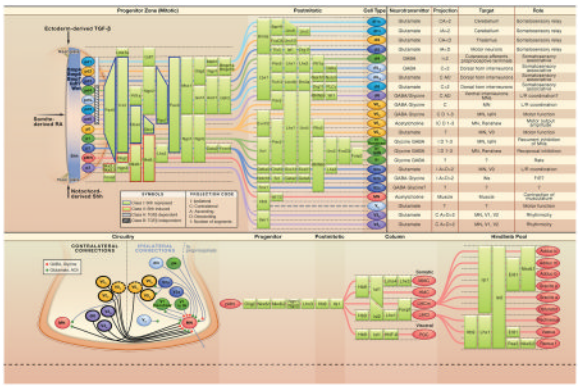

This SnapShot outlines the sequential genetic steps that generate neuronal diversity within an idealized spinal segment of the mouse. The progression from neural progenitor cells to postmitotic neurons spanning embryonic day 9.5 (e9.5) to e18.5 is shown from left to right, although some events are not strictly linear. Diverse combinations of Hox transcription factor expression along the rostrocaudal (i.e., head-to-tail) axis further subdivide motor neurons, but for clarity, these patterns are not reflected in this idealized segment. Recent studies have begun to define the functions of the cardinal cell types in the spinal cord, particularly those that relate to locomotor behaviors.

Precursor Generation

Cellular identities are defined by the influence of a two-dimensional coordinate system of morphogen gradients that act on the neuroepithelial cells occupying the ventricular zone of the ~e9.5 neural tube. A Sonic hedgehog (Shh) gradient produced by the notochord and the floor plate establishes the identity of five ventral progenitor cell domains (p0, p1, p2, pMN, and p3), marked by the expression transcription factors with a basic-helix-loop-helix (bHLH) domain and a homeodomain. Genes repressed by Shh are categorized as class I (e.g., *Irx3*), and genes induced by Shh are termed class II (e.g., *Olig2*). Typically, the transcription factors in adjacent progenitor domains repress expression of factors in neighboring domains, preventing cells from developing with hybrid identities. Transforming growth factor β (TGFβ) family proteins from the overlying ectoderm (e.g., *Bmp4*) and roof plate (e.g., *Gdnf7*) produces dorsalizing signals. The dorsal-most progenitor domains, pd1–pd3, depend on TGFβ, whereas pd4–pd6 and pdIL are independent of TGFβ. The somite produces retinoic acid (RA) that controls subtype and dorsoventral identity through *Pax6*. Within this idealized segment of spinal cord, these morphogen gradients establish 12 progenitor domains that grossly give rise to seven dorsal interneuron progenitor divisions, pd1–6 and pdIL; four ventral interneuron progenitor divisions, p0–3; and one motor neuron progenitor domain, pMN. Ventral progenitor domains (e.g., pMN) produce one cell type early (e.g., motor neurons) followed by another cell type later (e.g., oligodendrocytes).

Refinement and Subdivision of Classes

As cells mature within their respective progenitor zones and begin to exit the cell cycle, an abrupt transition occurs in the transcriptional profile of cells. The postmitotic cells from some progenitor domains (e.g., p2) become further diversified through intercellular signaling interactions (e.g., Notch-Delta), which leads to the generation of excitatory V2a and inhibitory V2b neurons from common ancestral progenitor cells. As neuron development progresses, the neurotransmitter properties of the cells emerge, and they express phenotypic markers, such as neurotransmitter biosynthetic enzymes (e.g., choline acetyltransferase [*ChAT*] or glutamic acid decarboxylase [*GAD*]) and vesicular transport proteins (e.g., *vGluT2*). Many progenitor domains tend to give rise to neurons with similar initial axonal growth trajectories; however, the pd1, p1, and p0 domains produce interneuron subtypes with diverse axonal projections, which are clear exceptions to this trend. The diversification of a single neuronal class is best exemplified by motor neurons.

Motor Neurons

Motor neurons are subdivided by their cell body positions within motor columns. Each motor column consists of multiple motor pools that innervate individual muscles. Generic postmitotic motor neurons become subdivided into the medial and hypaxial motor columns (MMC and HMC), which innervate the back (epaxial) and trunk (hypaxial) musculature, respectively. At limb levels, the medial and lateral portions of the lateral motor column (LMCm and LMCl) innervate the ventral and dorsal portions of the limb, respectively. Additional motor neurons form the autonomic nervous system as preganglionic (PGC) cholinergic neurons of sympathetic and parasympathetic targets. Pools of motor neurons innervating the same muscle can be defined by unique combinations of transcription factors (e.g., *Nkx6* and *Ets* classes).

Locomotor Circuitry

The spinal interneurons and motor neurons comprise a central pattern-generating circuitry that is capable of producing rhythmic left-right and flexor-extensor alternation in isolated cords, called fictive locomotion. Molecular genetic studies have defined roles for several classes of interneurons found in the ventral cord. Mutant mice lacking contralat-erally projecting inhibitory *Dbx1*$^+$ V0 class interneurons display a disorganized left-right alternation. Use of diphtheria toxin to ablate ipsilaterally projecting excitatory *Chx10*$^+$ V2a cells also disturbs right-left alternation and, notably, at higher speeds, animals transition to a left-right synchronous gallop that is not seen in wild-type mice. Loss or inactivation of ipsilateral inhibitory *En1*$^+$ V1 neurons results in a marked slowing of locomotion, whereas inactivation of contralaterally projecting excitatory *Sim1*$^+$ V3 interneuron class disrupts the regularity of the rhythm. Inactivation of the *Pitx2*$^+$ $V0_C$ class disrupts locomotion during swimming due to altered integration of sensory feedback. The ipsilaterally projecting glutamatergic *Hb9*$^+$ V_x class is rhythmically active during locomotion. The *Ptf1a*$^+$ dI4 class forms inhibitory presynaptic contacts on glutamatergic proprioceptive sensory neurons in the ventral spinal cord. The dI6 and dI3 interneuron classes make direct connections onto motor neurons; however, their roles have not been determined.

Abbreviations

Ascl1	achaete-scute complex homolog 1 (*Drosophila*)
BarH1	BarH-like homeobox
Bhlhb5	basic-helix-loop-helix family, member e22

Bmp2	bone morphogenetic protein 2
Bmp4	bone morphogenetic protein 4
Bmp5	bone morphogenetic protein 5
Bmp6	bone morphogenetic protein 6
Bmp7	bone morphogenetic protein 7
Bmpr1a	bone morphogenetic protein receptor, type 1a
Bmpr1b	bone morphogenetic protein receptor, type 1b
Brn3a	POU domain, class 4, transcription factor 1
Chx10	visual system homeobox
Dbx1	developing brain homeobox
Dbx2	developing brain homeobox
Isl1	ISL1 transcription factor, LIM homeodomain
Isl2	ISL2 transcription factor, LIM homeodomain
Lbx1	ladybird homeobox homolog 1
Lhx1	LIM homeobox protein 1
Lhx2	LIM homeobox protein 2
Lhx4	LIM homeobox protein 4
Lhx5	LIM homeobox protein 5
Lhx9	LIM homeobox protein 9
Lmo4	LIM domain only 4
Lmx1b	LIM homeobox transcription factor 1 beta
Math1	atonal homolog 1 (*Drosophila*)
Msx1	homeobox, msh-like 1
Ngn1	neurogenin 1
Ngn2	neurogenin 2
Ngn3	neurogenin 3
Notch	Notch gene homolog 1 (*Drosophila*)
Nkx2.2	NK2 transcription factor related locus 2
Nkx2.9	NK2 transcription factor related, locus 9
Nkx6.1	NK6 homeobox 1
Nkx6.2	NK6 homeobox 2
Olig2	oligodendrocyte transcription factor 2
Olig3	oligodendrocyte transcription factor 3
Pax2	paired box gene 2
Pax3	paired box gene 3
Pax6	paired box gene 6

Pax7	paired box gene 7
PLCgamma	phospholipase C, gamma 1
Ptf1a	pancreas-specific transcription factor 1a
Pitx2	paired-like homeodomain transcription factor 2
RA	retinoic acid
Scl	T cell acute lymphocytic leukemia 1
Shh	Sonic hedgehog
Sim1	single-minded homolog 1
Sox1	SRY box-containing gene 1
Sox14	SRY box-containing gene 14
Sox21	SRY box-containing 21
Tlx1/3	T cell leukemia, homeobox 1/3
Wt1	Wilms tumor homolog 1

References

1. Dasen JS, Jessell TM. Hox networks and the origins of motor neuron diversity. Curr Top Dev Biol. 2009; 88:169–200. [PubMed: 19651305]
2. Goulding M. Circuits controlling vertebrate locomotion: moving in a new direction. Nat Rev Neurosci. 2009; 10:507–518. [PubMed: 19543221]
3. Goulding M, Pfaff SL. Development of circuits that generate simple rhythmic behaviors in vertebrates. Curr Opin Neurobiol. 2005; 15:14–20. [PubMed: 15721739]
4. Grillner S, Jessell TM. Measured motion: searching for simplicity in spinal locomotor networks. Curr Opin Neurobiol. 2009; 19:572–586. [PubMed: 19896834]
5. Helms AW, Johnson JE. Specification of dorsal spinal cord interneurons. Curr Opin Neurobiol. 2003; 13:42–49. [PubMed: 12593981]
6. Jankowska E. Spinal interneuronal systems: identification, multifunctional character and reconfigurations in mammals. J Physiol. 2001; 533:31–40. [PubMed: 11351010]
7. Jessell TM. Neuronal specification in the spinal cord: inductive signals and transcriptional codes. Nat Rev Genet. 2000; 1:20–29. [PubMed: 11262869]
8. Kiehn O. Locomotor circuits in the mammalian spinal cord. Annu Rev Neurosci. 2006; 29:279–306. [PubMed: 16776587]
9. Ladle DR, Pecho-Vrieseling E, Arber S. Assembly of motor circuits in the spinal cord: driven to function by genetic and experience-dependent mechanisms. Neuron. 2007; 56:270–283. [PubMed: 17964245]
10. Lee SK, Pfaff SL. Transcriptional networks regulating neuronal identity in the developing spinal cord. Nat Neurosci. 2001; 4(Suppl):1183–1191. [PubMed: 11687828]