neurogenesis. We have uncovered a cell autonomous circuit that regulates the transition from low to high proneural gene expression required to initiate neuronal differentiation. This circuit is mediated by a ubiquitin adaptor protein that targets the degradation of a widely expressed inhibitor of proneural gene expression.

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Program/Abstract # 15
Sequential neuropilin receptor signaling guides neural crest and motor axon segmentation
Laura S. Gammill, Julaine Roffers-Agarwal
Department of Genetics, Cell Biology and Development, U of MN, Minneapolis, MN 55455, USA

In the vertebrate trunk, segmentally iterated ganglia and nerves connect the spinal cord with the periphery through the protective vertebral. Peripheral nervous system (PNS) segmentation is initiated by ventrally migrating neural crest cells that exclusively invade the anterior sclerotome and differentiate into metameric sensory dorsal root ganglia (DRG) and sympathetic ganglia. Meanwhile, motor axons project from the ventral spinal cord through the somites in a segmental fashion, joining sensory projections to create metameric mixed spinal nerves. The signaling pathways that direct PNS segmentation are unclear. Neuropilin 2 (Nrp2)/Semaphorin 3F (Sema3F) signaling is required for segmental neural crest migration, but not for metameric DRGs, indicating that a second signal patterns gangliogenesis. We show that Nrp1 signaling through Sema3A (Nrp1Sema3A) is that second signal, as Nrp2/Nrp1Sema3A double mutant mice exhibit fused DRGs. While Nrp1Sema3A−/− DRGs are metameric, this is likely because Nrp2/Sema3F segments migratory neural crest cells prior to ganglia formation. Based on phased expression of Sema3F and Sema3A in the posterior sclerotome, we infer a sequential, non-redundant requirement for these pathways during sensory development. Furthermore, we demonstrate that Nrp2 and Nrp1 are sequentially required during segmental motor axon outgrowth and spinal nerve fasciculation as well. Together, our data show that a cascade of Nrp-dependent events segment both sensory and motor components of the trunk PNS, and reveal for the first time that the same signaling pathways govern both sensory and motor metamersism.

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Program/Abstract # 16
Antagonistic actions of Olig2 and the Notch signaling pathway in the assignment of neuronal and glial cell fates
Lin Lin Yanga, Zachary B. Gabera, Steven E. Weickse, Eric Dessaudc, David L. Rousseoa, James Briscoeb, Bennett G. Novitcha

aDepartment of Neurobiology and Broad Center of Regenerative Medicine and Stem Cell Research, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
bDepartment of Cell and Developmental Biology, University of Michigan, Ann Arbor, MI, USA
cDevelopmental Neurobiology, National Institute for Medical Research Mill Hill, London, UK

Throughout the developing nervous system, differentiated neurons and glial cells are formed in a spatially and temporally coordinated manner. To gain insights into this process, we have been studying the mechanisms by which neural stem and progenitor cells sequentially give rise to motor neurons and oligodendrocytes in the ventral spinal cord. Our findings indicate that the early neurogenic phase of motor neuron differentiation is orchestrated by the bHLH transcription factor Olig2 through inhibitory interactions with the Notch signaling pathway. Olig2 directly binds and represses the expression of the Notch pathway effectors Hes 1 and Hes5 to promote motor neuron differentiation. Later in development, activation of the Notch pathway in turn alters the response of neural progenitors to Sonic Hedgehog (Shh) signaling, leading to changes in Olig2 expression and the formation of specific glial cell types. Together, these findings suggest a novel point of intersection between Olig2 and both the Notch and Shh signaling pathways, and demonstrate how the reiterative use of these pathways can result in the assignment of neuronal and glial cell fates.

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