front-loading genes involved in heat stress [8,19], employing rapid acclimatization pathways [7,18,19], changing the composition of their algal symbiont communities [14,15], and maintaining a healthy pool of microbial associates [10] to prevent infection and disease during recovery from heat stress. Despite catastrophic losses over the last few decades and the recent listing of 20 additional coral species under the U.S. Endangered Species Act, these diverse responses provide hope that the world's remaining corals may still contain the adaptive ingredients needed to survive. For these enigmatic chimeras — part animal, part alga, part microbial and viral consortium — the power that prevails may well be both polygenic and polygenomic.

References

1. Jackson, J.B.C., Donovan, M.K., Cramer, K.L., Lam, V.Y.Y., Bak, R.P.M., Chollett, I., Connolly, S.R., Cortes, J., Dustan, P., Eakin, C.M., *et al*. (2014). Part I: Overview and synthesis for the wider Caribbean region. In Status and Trends of Caribbean Coral Reefs: 1970-2012 (Global Coral Reef Monitoring Network), pp. 55–154.
2. Bruno, J.F., and Selig, E.R. (2007). Regional decline of coral cover in the Indo-Pacific: timing, extent, and subregional comparisons. PLoS One *2*, e711, 711–718.
3. De'ath, G., Fabricius, K.E., Sweatman, H., and Puotinen, M. (2012). The 27-year decline of coral cover on the Great Barrier Reef and its causes. Proc. Natl. Acad. Sci. USA *109*, 17995–17999.
4. Lesser, M.P., Bythell, J.C., Gates, R.D., Johnstone, R.W., and Hoegh-Guldberg, O. (2007). Are infectious diseases really killing corals? Alternative interpretations of the experimental and ecological data. J. Exp. Mar. Biol. Ecol. *346*, 36–44.
5. Hoegh-Guldberg, O., Mumby, P.J., Hooten, A.J., Steneck, R.S., Greenfield, P., Gomez, E., Harvell, C.D., Sale, P.F., Edwards, A.J., Caldeira, K., *et al*. (2007). Coral reefs under rapid climate change and ocean acidification. Science *318*, 1737–1742.
6. Bay, R.A., and Palumbi, S.R. (2014). Multi-locus adaptation associated with heat resistance in reef-building corals. Curr. Biol. *24*, 2952–2956.
7. Palumbi, S.R., Barshis, D.J., Traylor-Knowles, N., and Bay, R.A. (2014). Mechanisms of reef coral resistance to future climate change. Science *344*, 895–898.
8. Barshis, D.J., Ladner, J.T., Oliver, T.A., Seneca, F.O., Traylor-Knowles, N., and Palumbi, S.R. (2013). Genomic basis for coral resilience to climate change. Proc. Natl. Acad. Sci. USA *110*, 1387–1392.
9. Rohwer, F., Seguritan, V., Azam, F., and Knowlton, N. (2002). Diversity and distribution of coral-associated bacteria. Mar. Ecol. Pro. Ser. *243*, 1–10.
10. Bourne, D.G., Garren, M., Work, T.M., Rosenberg, E., Smith, G.W., and Harvell, C.D. (2009). Microbial disease and the coral holobiont. Trends Microbiol. *17*, 554–562.
11. Glynn, P.W. (1993). Coral reef bleaching - ecological perspectives. Coral Reefs *12*, 1–17.
12. Coles, S.L., Jokiel, P.L., and Lewis, C.R. (1976). Thermal tolerance in tropical versus subtropical Pacific reef corals. Pac. Sci. *30*, 159–166.
13. Wilkinson, C.R., ed. Status of Coral Reefs of the World: 2004 (Cape Ferguson, Queensland: Australian Institute of Marine Science).
14. Baker, A.C., Starger, C.J., McClanahan, T.R., and Glynn, P.W. (2004). Corals' adaptive response to climate change. Nature *430*, 741.
15. Berkelmans, R., and van Oppen, M.J.H. (2006). The role of zooxanthellae in the thermal tolerance of corals: a 'nugget of hope' for coral reefs in an era of climate change. Proc. Soc. B. Biol. Sci. *273*, 2305–2312.
16. Jones, A.M., Berkelmans, R., Van Oppen, M.J.H., Mieog, J.C., and Sinclair, W. (2008). A community change in the algal endosymbionts of a scleractinian coral following a natural bleaching event: field evidence of acclimatization. Proc. Soc. B. Biol. Sci. *275*, 1359–1365.
17. Granados-Cifuentes, C., Bellantuono, A.J., Ridgway, T., Hoegh-Guldberg, O., and Rodriguez-Lanetty, M. (2013). High natural gene expression variation in the reef-building coral *Acropora millepora*: potential for acclimative and adaptive plasticity. BMC Genomics *14*, 228.
18. DeSalvo, M.K., Sunagawa, S., Voolstra, C.R., and Medina, M. (2010). Transcriptomic responses to heat stress and bleaching in the elkhorn coral *Acropora palmata*. Mar. Ecol. Prog. Ser. *402*, 97–113.
19. Kenkel, C.D., Meyer, E., and Matz, M.V. (2013). Gene expression under chronic heat stress in populations of the mustard hill coral (*Porites astreoides*) from different thermal environments. Mol. Ecol. *22*, 4322–4334.
20. Silverstein, R.N., Cunning, R., and Baker, A.C. (2014). Change in algal symbiont communities after bleaching, not prior heat exposure, increases heat tolerance of reef corals. Glob. Chang. Biol. http://dx.doi.org/10.1111/gcb.12706.

Department of Marine Biology and Ecology, Rosenstiel School of Marine and Atmospheric Science, University of Miami, 4600 Rickenbacker Causeway, Miami, FL 33149, USA.
E-mail: abaker@rsmas.miami.edu

http://dx.doi.org/10.1016/j.cub.2014.11.014

Synaptic Specificity: When the Neighbors Are Away, Sensory Axons Turn Promiscuous

A new study describes cellular mechanisms establishing synaptic specificity during development and remodeling of a zebrafish mechanosensory organ. Coordination amongst postsynaptic neurons and interactions between presynaptic and postsynaptic cells together promote the segregation of circuits responding to distinct sensory stimuli.

Donald P. Julien and Alvaro Sagasti*

During development the numerous and diverse neurons of the brain select specific synaptic targets with which to form precise circuits underlying perception, behavior, and cognition. Circuits can remodel by modifying synaptic connectivity, allowing the brain to learn, adapt to environmental changes, and repair damaged circuitry. Sensory cells exposed to the external environment, such as mammalian olfactory and gustatory receptors, are particularly vulnerable to damage that requires continuous cellular replacement and the re-establishment of synaptic connections (reviewed in [1,2]). Ensuring reliable transmission of information about the quality and location of sensory stimuli during remodeling requires mechanisms for re-establishing correct connectivity from primary sensory receptors to their synaptic partners. In this issue of *Current Biology*, Pujol-Martí *et al.* [3] describe an interaction between sensory neurons that promotes the formation of appropriate connections in the zebrafish lateral line system. This interaction contributes to both the establishment of synaptic specificity during development and its restoration during remodeling, despite frequent sensory cell turnover.

In fish and amphibians the lateral line sensory system detects local vibrations and water movement beginning at early developmental stages (reviewed in [4]). This sensory information is essential for complex behaviors, such as navigation, and for motor responses to other fish, prey, and predators. Translation of water motion into neuronal signals is accomplished by sensory organs called neuromasts, which are studded across the head and body. In larval

zebrafish each neuromast contains roughly 10–20 mechanosensory hair cells that are structurally similar to the hair cells of the mammalian inner ear: each extends an apical bundle of actin-based stereocilia that is apposed to a single microtubule-based kinocilium. Deflection of the hair bundle towards the kinocilium depolarizes the cell, whereas deflection away from the kinocilium hyperpolarizes it. Individual neuromasts are innervated by 2–4 afferent axons of lateral line neurons that receive synaptic inputs from hair cells. Each neuromast contains two distinct hair cell populations with apical stereocilia oriented in opposite directions, causing them to respond to stimulation from different directions. Lateral line axon terminals extend throughout the neuromast but only form synapses with roughly half of its hair cells. These synapses are selective for hair cells of a particular orientation [5,6], and thus fire preferentially to deflections from one direction [3,7]. The simplicity and precision of synaptic connectivity in the zebrafish lateral line make it an appealing system for uncovering the rules governing the formation and re-establishment of synaptic specificity.

How do lateral line afferents choose to connect exclusively with hair cells of a specific orientation? One possibility is that afferent axons instruct hair cells to adopt a particular polarity. This model, however, is unlikely, since hair cell polarity forms normally in the absence of innervating afferents [3,6]. Alternatively, sensory neurons could be genetically specified to strictly select hair cells of a particular orientation as synaptic partners. This model predicts that the synaptic selectivity of any particular sensory afferent is independent of other afferents. Pujol-Martí *et al.* [3] tested this prediction by removing all but one afferent innervating a particular neuromast, using genetic and surgical methods. Surprisingly, solitary afferents deprived of neighbors lost their specificity and promiscuously innervated hair cells of both polarities (Figure 1). When neighboring neurons were allowed to regenerate and reinnervate the neuromast, promiscuous afferents re-established their selectivity. These results demonstrate that the selective pattern of connectivity in the lateral line requires interactions not only between axons and hair cells, but also amongst different axons innervating a neuromast. In other words, afferents possess a latent ability to receive synapses from any hair cell in a neuromast; their preference for hair cells of a particular polarity only emerges from interactions with other lateral line afferents.

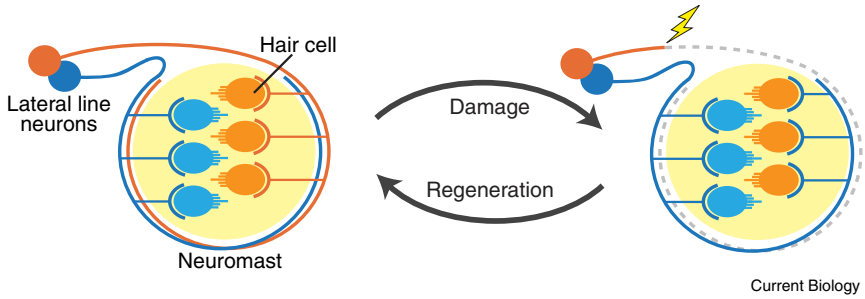

Figure 1. Interactions between neighboring postsynaptic neurons establish and maintain synaptic specificity in the zebrafish lateral line sensory system.

Zebrafish neuromasts contain mechanosensory hair cells of two opposite orientations (blue and orange). Intact neuromasts are innervated by multiple lateral line afferents, each of which receives synapses exclusively from hair cells of a particular orientation (left). When an afferent neuron is deprived of neighbors it promiscuously innervates hair cells of both types (right), but regeneration of the neighbors restores coherent innervation.

At first glance, the expansion of synaptic territory by isolated lateral line neurons resembles the well-described competitive innervation process that occurs during synaptic refinement at the neuromuscular junction (NMJ), where removing axons allows neighboring terminals to expand [8]. However, several features of synaptic refinement in the lateral line distinguish it from this classic model. For instance, lateral line axons do not appear to compete for innervation territory. On the contrary, branches of axons with different orientation preferences overlap freely during development. Although the removal of neighbors allows for isolated axons to form promiscuous synapses, it does not affect the dynamics or complexity of the axonal terminal arbors [3]. Additionally, the end result of synaptic competition at the NMJ is an arrangement in which each muscle fiber receives innervation from a single, 'winning' axon [9]. In the lateral line a single axon does not always win exclusive access to all hair cells of a particular orientation. Labeling two neighboring afferents with different fluorescent proteins clearly demonstrated that most hair cells are innervated by more than one axon [3]. Thus, although afferent axons are strict selectors of hair cell polarity, hair cells are not strict selectors of afferent axons. These findings suggest that there are at least two subtypes of lateral line afferents capable of forming synapses with hair cells of either orientation, despite having a preference for one. Afferents of the same subtype can innervate multiple hair cells of their preferred orientation, but prevent hair cells from synapsing onto neighbors of the other subtype.

Neuronal activity often contributes to the selection of synaptic partners from multiple presynaptic or postsynaptic options [10]. At the NMJ, synchronous firing between the presynaptic motor neuron and the postsynaptic muscle fiber is critical for stabilizing a single axon and destabilizing its neighbors [9]. Lateral line afferents could potentially use the differences in sensory-evoked activity between the two types of hair cells to stabilize only coherent synapses and avoid incoherent ones. However, several lines of evidence suggest that activity is not required for establishing lateral line orientation selectivity. Electrophysiological recordings from isolated afferents receiving input from hair cells of both orientations confirmed that these new synapses are capable of driving postsynaptic action potentials, demonstrating that afferent axons can tolerate incoherent synapses [3]. Moreover, the authors corroborated a previous finding that orientation selectivity is maintained in mutants lacking hair cell mechanotransduction [3,11]. Together these findings demonstrate that presynaptic activity is not required for lateral line orientation selectivity and imply that lateral line afferents rely instead on molecular cues to restrict their synaptic territories.

Previous studies found that individual lateral line axons reliably re-establish connections with hair cells of the same orientation following repeated rounds of hair cell ablation and regeneration, indicating that afferents retain a 'memory' of hair cell polarity after denervation [5,6]. The current study suggests that this memory is at least partially maintained by inhibitory interactions between neighboring lateral line axons [3]. A similar strategy of "synaptic tiling" occurs between neighboring DA8 and DA9 motor neurons in *Caenorhabdities elegans* [12]. Much like lateral line afferents, DA8 and DA9 axons are closely associated with one another in the dorsal nerve cord, but segregate their synapses into adjacent, non-overlapping synaptic zones in an activity-independent manner. Additionally, the synaptic zones of both axons expanded in worms that had one axon genetically displaced from the dorsal nerve cord, suggesting that axons mutually inhibit the expansion of each other's synaptic territory. The marked similarities between these different species and neural systems raise the possibility that synaptic tiling may be a conserved mechanism for establishing and maintaining patterns of neural connectivity.

Although Pujol-Martí *et al.* [3] elegantly demonstrated that neighboring lateral line axons restrict each other's synaptic territories, the molecular signals underlying this regulation are unknown. Synaptic tiling between *C. elegans* motor axons requires plexin-1 and semaphorin-1 expression in DA9 motor neurons to segregate synapses [12]. Similarly, semaphorin signaling is required for restricting or eliminating synapses in the mouse spinal cord, hippocampus, and striatum [13–15]. In addition to negative regulators, positive synaptogenic interactions between hair cells and afferents are also likely required for establishing and maintaining lateral line circuitry. The molecules that mediate these interactions are also unknown, but lateral line axons with different orientation preferences could express different cell surface adhesion molecules (reviewed in [16,17]) that prefer binding partners differentially enriched in each hair cell population. Identifying the proteins mediating positive cellular interactions between lateral line neurons and hair cells, as well as negative interactions between neighboring afferent neurons with different preferences, will provide a molecular paradigm for the segregation and maintenance of neural circuits responding to distinct sensory stimuli.

References

1. Brann, J.H., and Firestein, S.J. (2014). A lifetime of neurogenesis in the olfactory system. Front. Neurosci. *8*, 182.
2. Feng, P., Huang, L., and Wang, H. (2014). Taste bud homeostasis in health, disease, and aging. Chem. Senses *39*, 3–16.
3. Pujol-Marti, J., Faucherre, A., Aziz-Bose, R., Asgharsharghi, A., Colombelli, J., Trapani, J.G., and Lopez-Schier, H. (2014). Converging axons collectively initiate and maintain synaptic selectivity in a constantly remodeling sensory organ. Curr. Biol. *24*, 2968–2974.
4. Pujol-Martí, J., and López-Schier, H. (2013). Developmental and architectural principles of the lateral-line neural map. Front. Neural Circuits *7*, 47.
5. Faucherre, A., Pujol-Martí, J., Kawakami, K., and López-Schier, H. (2009). Afferent neurons of the zebrafish lateral line are strict selectors of hair-cell orientation. PLoS One *4*, e4477.
6. Nagiel, A., Andor-Ardó, D., and Hudspeth, A.J. (2008). Specificity of afferent synapses onto plane-polarized hair cells in the posterior lateral line of the zebrafish. J. Neurosci. *28*, 8442–8453.
7. Obholzer, N., Wolfson, S., Trapani, J.G., Mo, W., Nechiporuk, A., Busch-Nentwich, E., Seiler, C., Sidi, S., Söllner, C., Duncan, R.N., *et al.* (2008). Vesicular glutamate transporter 3 is required for synaptic transmission in zebrafish hair cells. J. Neurosci. *28*, 2110–2118.
8. Walsh, M.K., and Lichtman, J.W. (2003). In vivo time-lapse imaging of synaptic takeover associated with naturally occurring synapse elimination. Neuron *37*, 67–73.
9. Darabid, H., Perez-Gonzalez, A.P., and Robitaille, R. (2014). Neuromuscular synaptogenesis: coordinating partners with multiple functions. Nat. Rev. Neurosci. *15*, 703–718.
10. Okawa, H., Hoon, M., Yoshimatsu, T., Della Santina, L., and Wong, R.O.L. (2014). Illuminating the multifaceted roles of neurotransmission in shaping neuronal circuitry. Neuron *83*, 1303–1318.
11. Nagiel, A., Patel, S.H., Andor-Ardó, D., and Hudspeth, A.J. (2009). Activity-independent specification of synaptic targets in the posterior lateral line of the larval zebrafish. Proc. Natl. Acad. Sci. USA *106*, 21948–21953.
12. Mizumoto, K., and Shen, K. (2013). Interaxonal interaction defines tiled presynaptic innervation in C. elegans. Neuron *77*, 655–666.
13. Pecho-Vrieseling, E., Sigrist, M., Yoshida, Y., Jessell, T.M., and Arber, S. (2009). Specificity of sensory-motor connections encoded by Sema3e-Plxnd1 recognition. Nature *459*, 842–846.
14. Liu, X.-B., Low, L.K., Jones, E.G., and Cheng, H.-J. (2005). Stereotyped axon pruning via plexin signaling is associated with synaptic complex elimination in the hippocampus. J. Neurosci. *25*, 9124–9134.
15. Ding, J.B., Oh, W.-J., Sabatini, B.L., and Gu, C. (2011). Semaphorin 3E–Plexin-D1 signaling controls pathway-specific synapse formation in the striatum. Nat. Neurosci. *15*, 215–223.
16. Williams, M.E., de Wit, J., and Ghosh, A. (2010). Molecular mechanisms of synaptic specificity in developing neural circuits. Neuron *68*, 9–18.
17. Margeta, M.A., and Shen, K. (2010). Molecular mechanisms of synaptic specificity. Mol. Cell. Neurosci. *43*, 261–267.

Department of Molecular, Cell, and Developmental Biology, UCLA, Los Angeles, CA 90095-1606, USA.
*E-mail: sagasti@mcdb.ucla.edu

http://dx.doi.org/10.1016/j.cub.2014.11.004

ER Morphology: Sculpting with XendoU

Endoplasmic reticulum (ER) sheet membranes are covered with ribosomes and RNAs that are involved in protein synthesis. A new study reveals that a calcium-activated endoribonuclease of the EndoU protein family promotes the formation of tubular ER networks, contributing to dynamic shaping of the ER in cells.

Guohua Zhao and Craig Blackstone*

The endoplasmic reticulum (ER) is a continuous membrane system comprising the nuclear envelope, flat sheets often studded with ribosomes, and a polygonal network of mostly smooth tubules extending throughout the cell. Synthesis, modification, and transport of lipids and proteins as well as Ca^{2+} sequestration and protein quality control within the ER have been extensively investigated over many years, but mechanisms responsible for the distinctive morphology of the ER have only been uncovered more recently [1,2]. Several eukaryotic protein families, including reticulons and REEPs/DP1/Yop1p, harbor hydrophobic hairpin domains that partially insert into the lipid bilayer, shaping high-curvature ER tubules [3]. Members of the atlastin/RHD3/Sey1p family of large, membrane-bound GTPases