Feature Review

CellPress

Special Issue: Circuit Development and Remodeling

Neuronal remodeling in retinal circuit assembly, disassembly, and reassembly

Florence D. D'Orazi*, Sachihiro C. Suzuki*, and Rachel O. Wong

Department of Biological Structure, University of Washington, 1959 NE Pacific Street, Seattle, WA 98195, USA

Developing neuronal circuits often undergo a period of refinement to eliminate aberrant synaptic connections. Inappropriate connections can also form among surviving neurons during neuronal degeneration. The laminar organization of the vertebrate retina enables synaptic reorganization to be readily identified. Synaptic rearrangements are shown to help sculpt developing retinal circuits, although the mechanisms involved remain debated. Structural changes in retinal diseases can also lead to functional rewiring. This poses a major challenge to retinal repair because it may be necessary to untangle the miswired connections before reconnecting with proper synaptic partners. Here, we review our current understanding of the mechanisms that underlie circuit remodeling during retinal development, and discuss how alterations in connectivity during damage could impede circuit repair.

Making and breaking connections

The assembly of neuronal circuits during development involves cellular and molecular processes that are orchestrated at multiple levels. Component cell types need to be generated in the right numbers and positioned at their final locations. Each cell type must then elaborate axons and dendrites to connect with suitable synaptic partners, and establish the mature number, type, and distribution of synapses. Also, synaptic machinery has to be localized appropriately, and the molecular composition unique to each synapse type must be attained to ensure proper function. Often, these developmental events involve several steps of refinement before circuits are fully established. For example, axonal and dendritic arbors may undergo pruning to achieve their final patterns, and the molecular compositions at synapses may be reconfigured before maturation. Here, we review our current understanding of the cellular strategies and molecular mechanisms that underlie the structural and functional remodeling events that organize circuits during development. Further, we highlight the structural and synaptic reorganization that take place in disease conditions, and consider how these rearrangements could potentially impact circuit repair. We will focus on the vertebrate retina for which organization and function are relatively well understood, and for which circuit deconstruction and dysfunction can be probed in detail using anatomical and physiological techniques.

Remodeling and retinal circuit assembly

Organizing synaptic laminae

The laminar organization of the vertebrate retina greatly facilitates investigation of circuit development. The vertebrate retina comprises five major classes of neurons that are arranged in three cellular layers (Figure 1A,B). Synaptic connections are organized into two layers, the outer (OPL) and the inner (IPL) plexiform layers. The IPL is

Glossary

Ionotropic glutamate receptors (iGluRs): : are glutamate-gated ion channels, and thus regulate fast excitatory transmission at ribbon synapses in the retina. The three major classes of iGluRs include *N*-methyl-D-aspartate (NMDA) receptors, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, and kainate (KA) receptors. Whereas NMDA receptors are primarily expressed in the IPL, AMPA and KA receptors are expressed in both the OPL and the IPL. The presence of AMPA or KA receptors at OFF-bipolar cell dendrites in the OPL allows these cells to depolarize in response to photoreceptor glutamate release in the dark [99].

Metabotropic glutamate receptors (mGluRs): : are expressed postsynaptically in most retinal neurons. Upon binding glutamate, mGluRs activate G-protein-dependent, second messenger cascades to convey the light signal. There are three groups of mGluRs, classified according to their secondary signaling cascades, pharmacology, and sequence homology. mGluR6, a group III mGluR, is expressed at ON-bipolar cell dendrites. Glutamate is normally released from photoreceptors in the dark, yet ON-bipolar cells depolarize in response to increments in light. Because glutamate binding of mGluR6 ultimately closes TRPM1 cation channels [100,101], ON-bipolar cells can 'sign-invert' the photoreceptor signal, and thus hyperpolarize in the dark and depolarize in response to increased illumination [99].

Ribbon synapses: : are excitatory synapses specialized for fast and tonic neurotransmitter release from photoreceptors and bipolar cells in the retina [1]. Unlike most neurons in the brain, photoreceptors and bipolar cells do not fire action potentials; instead they are tonically active, encoding sensory information with graded changes in their membrane potential. Ribbon synapses feature specialized structures in order to continuously release neurotransmitter vesicles in response to changes in membrane potential. In fact, ribbon synapses are named for their most prominent presynaptic structure, the ribbon, which appears as a large, electron-dense bar or sheet at the active zone of the synapse with electron microscopy. Synaptic vesicles containing glutamate are tethered to ribbons, and transmitter is released upon calcium-dependent exocytosis. Another specialization is evident at photoreceptor synapses, where the dendritic processes of horizontal cells and ON-bipolar cells invaginate the photoreceptor axonal terminal, placing postsynaptic glutamate receptors in close proximity to the presynaptic ribbon [102,103].

Corresponding author: Wong, R.O. (wongr2@uw.edu).

Keywords: retina; synapses; circuit refinement; retinal degeneration.

*These authors contributed equally.

0166-2236/

 http://dx.doi.org/10.1016/j.tins.2014.07.009

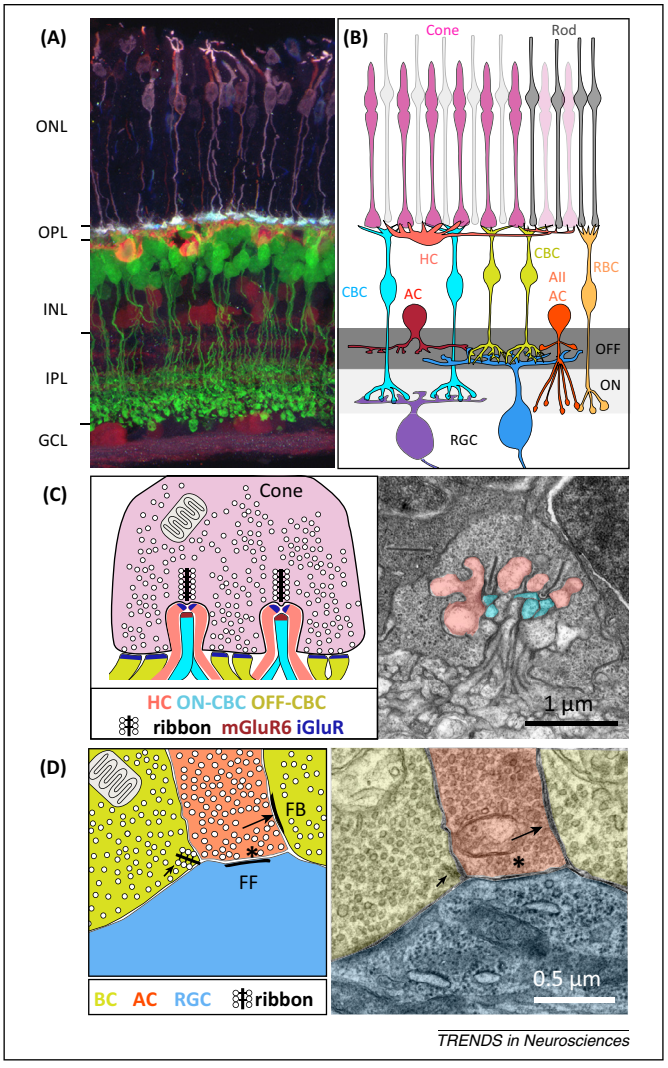

Figure 1. Organization of retinal structure, connectivity, and synapses. **(A)** Cross-section of the adult mouse retina (cover image from [7]). Cone photoreceptors (purple), horizontal cells (orange), bipolar cells (green), amacrine cells and retinal ganglion cells are labeled (red). ONL, outer nuclear layer; INL, inner nuclear layer; GCL, retinal ganglion cell layer; OPL, outer plexiform layer; IPL, inner plexiform layer. **(B)** Schematic showing major retinal pathways. Rod and cone photoreceptors detect changes in illumination, with rods functioning at low light levels, and cones at high light levels. Photoreceptor signals are conveyed by bipolar cells to retinal ganglion cells (RGCs). Cone bipolar cells (CBC) that largely contact cone photoreceptors are grouped into two major subclasses. Light increments depolarize ON-bipolar cells and hyperpolarize OFF-bipolar cells. ON and OFF synaptic connections are organized into separate laminae within the IPL. Horizontal cells (HC) and amacrine cells (AC) modulate information flow in the outer and inner retina, respectively. Rod bipolar cells (RBCs) predominantly convey rod input and contact AII amacrine cells (AII AC) that inhibit transmission from OFF-CBCs. **(C)** Subcellular organization of retinal synapses. Schematic of a cone photoreceptor ribbon synapse (left). ON-CBCs and HCs invaginate the cone pedicle at sites apposed to a ribbon structure with tethered synaptic vesicles. OFF-CBCs make basal contacts with the cone pedicle [104]. mGluR6, metabotropic glutamate receptors on ON BCs; iGluR, ionotropic glutamate receptor on OFF-CBCs. Electron micrograph of a zebrafish cone pedicle at 5 days post-fertilization (right, from Yoshimatsu *et al.* [20]). HC and CBC processes are pseudocolored as in the schematic. **(D)** Schematic (left) and ultrastructure (right) of synapses in the IPL of an adult mouse retina. Shown here are BC and AC synapses. A ribbon synapse (small arrow) between a CBC and an RGC is apparent. The AC here provides feed-forward (FF, asterisk) inhibition onto the RGC and feedback (FB, large arrow) inhibition onto the BC on the right. Micrograph provided by A. Bleckert [105].

further subdivided into two major sublayers. Within the inner (ON) sublamina lie the processes and connections of retinal ganglion cells (RGCs), bipolar cells, and amacrine cells that depolarize in response to increased illumination. Conversely, neurons that are hyperpolarized by light increments stratify their processes in the outer (OFF) sublamina. Specialized presynaptic structures called 'ribbons' mediate excitatory glutamatergic transmission in both plexiform layers [1] (see Glossary) (Figure 1C,D). Disruption to the layered organization of the retina greatly perturbs its function.

Several elegant studies have identified many guidance cues and adhesion molecules responsible for confining synaptic connectivity to the plexiform layers (summarized in Box 1). Structural and functional organization within each layer, however, can undergo further refinement during development before the adult circuitry emerges. In particular, early work in cat and ferret underscored the importance of structural remodeling in constraining the dendritic stratification of ON or OFF RGCs to their correct sublamina [2,3]. Initially, the dendrites of ON and OFF alpha and beta RGCs span the depth of the IPL. However, comparisons of fixed tissue across ages suggested that these RGC types constrain their dendrites within the ON or OFF sublamina after eliminating branches at inappropriate depths; failure to undergo such rearrangements leads to abnormal connectivity and function [4].

By contrast, recent studies in zebrafish and mice brought into question whether large-scale dendritic pruning is adopted universally by RGCs as a primary means to attain proper lamination. Fluorescent labeling of specific RGC types in transgenic mice [5] and time-lapse imaging in zebrafish [6] together revealed that RGCs employ several lamination strategies, which rely on dendritic remodeling to varying degrees: (i) large-scale refinement of an initially diffuse arbor; (ii) fine-scale refinement of an arbor that is biased to the ON or OFF layer (i.e., pruning within a layer); and (iii) sequential loss or (iv) addition of an entire arbor or arbors (Figure 2). It is not known why RGCs adopt diverse strategies. However, it is clear that the extent of remodeling is not correlated with specific features of the RGCs, such as ON versus OFF function or the number of arbors, nor is it species-dependent.

Retinal neurons other than RGCs also undergo neurite remodeling to varying degrees to achieve their final lamination patterns. Mouse rod bipolar cells (RBCs) and ON-cone bipolar cells (ON-CBCs) extend axonal processes from a neuroepithelial-like stalk that eventually retracts as the axonal terminal elaborates. Lateral axonal growth is confined to the ON sublamina, suggesting that these bipolar cells do not undergo significant remodeling to target their major synaptic layer [7]. Whether fine-scale refinement occurs to further restrict the axonal terminals of the 10 or more types of mouse bipolar cells [8,9] to their respective layer within the IPL remains unknown. Similarly, migrating amacrine cells that are initially multi-polar preferentially direct neurite outgrowth toward the IPL and rapidly stratify once their somata reach their final location [10]. By contrast, rod and cone photoreceptor axons in the ferret retina transiently extend all the way into the IPL [11]. Simultaneous imaging of pre- and postsynaptic processes is now needed to ascertain how axonal and dendritic growth and remodeling are coordinated during development to establish the relevant connections.