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REVIEWS

Circuit Refinement in the Developing Nervous System: Uncovering the Molecular Mechanisms that Destabilize the Synapse

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Developing neural circuits undergo extensive refinement, characterized by the dynamic addition and removal of synapses. Localization of synaptic connections is critical for circuit architecture and information flow. Incorrect or excess synapses are eliminated to produce the precise cellular connections that are characteristic of mature nervous systems. This process has been observed across phylogeny, suggesting that the underlying mechanisms may be evolutionarily conserved. Studies of the vertebrate neuromuscular junction and visual circuitry have defined some overall themes in synapse refinement; the process is modulated by circuit activity and is commonly characterized by competition between inputs. The molecular networks that connect circuit activity to refinement are largely unknown, suggesting the need for a simpler model system. This review will examine the current understanding of synaptic refinement and introduce C. elegans as a model system to examine the molecular underpinnings of this complex, conserved process.

Keywords: *Synapse refinement, synaptic pruning, input elimination, synaptic remodeling, activity dependence, C. elegans, synapse disassembly, ubiquitination*

Critical period: Time interval during the development of an organism characterized by increased plasticity in the nervous system and an increased sensitivity to stimuli.

Heterochronic gene: Gene that controls the timing of development.

Introduction

During development, nervous systems create many more synapses than will be maintained at maturity[1]. It is unclear why this happens, but reduction involves large-scale removal of redundant synapses. The elimination of functional synapses is a hallmark of circuit refinement[2-4]. Studies of the neuromuscular junction (NMJ) have demonstrated that functional synapses are eliminated during circuit refinement[2-5]. Although it seems likely that functional synapses are also dismantled in the central nervous system, clear evidence of this phenomenon has been difficult to acquire[2-5]. Studies at the cerebellum show that incomplete elimination results in coordination defects in mice, suggesting that synapse elimination is important in creating functional neural circuits[6-8]. Synaptic refinement ranges from the disassembly of individual synapses to the complete removal of all connections between a presynaptic cell and its postsynaptic target[4,6]. The refinement of neural circuits has been observed in diverse organisms ranging from metamorphosis in insects to the development of the mammalian brain, indicating its evolutionary importance[1,9].

Synapse refinement is tightly regulated temporally[10-11]. Synapse elimination occurs in adults during injury or disease; however, this process is much more prevalent in the developing nervous system[12-13]. Extensive refinement occurs during critical periods of vertebrate development in the visual system, auditory system, cerebellum, and skeletal muscle[10-11]. Additionally, refinement is controlled temporally during the larval development of the invertebrate *C. elegans,* where the heterochronic gene *lin-14* controls the timing of GABAergic circuit remodeling[14].

Much of what we know about the process of synapse refinement has come from studies of the vertebrate NMJ, due to its simplicity and accessibility[15]. Models of central nervous system (CNS) refinement include the visual system circuitry and climbing fibers in the cerebellum[16]. Additionally, the simple nervous systems in *Drosophila* and *C. elegans* provide excellent models for molecular and genetic

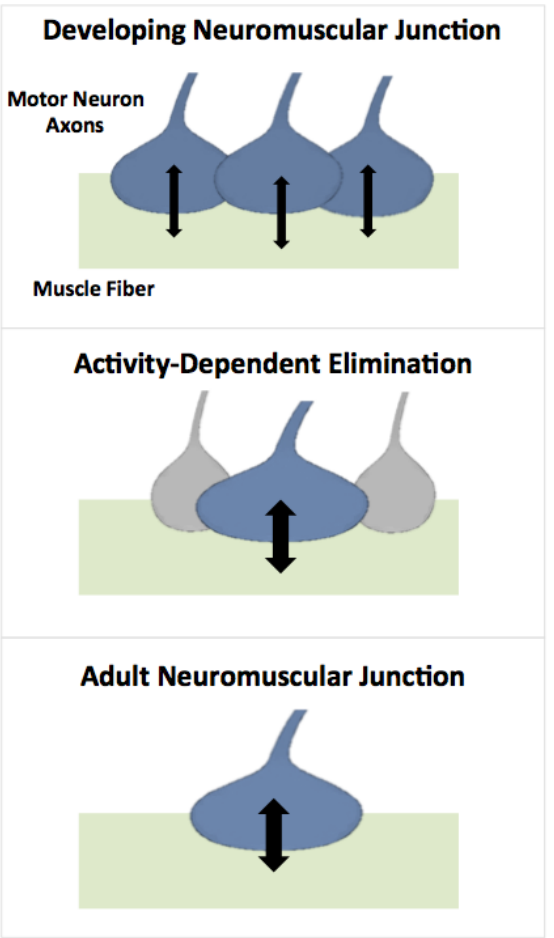

Figure 1: *Activity-dependent elimination at the neuromuscular junction (NMJ).* Initially, axons from multiple motor neurons innervate a single muscle fiber. Activity-dependent elimination results in the strengthening of one synapse (blue), while the other inputs become weaker and are eliminated (gray).

manipulation[17-18]. Our current understanding from studying these diverse model systems has led to overarching themes in synapse refinement, highlighted below.

Synaptic Activity and Circuit Refinement

Early studies of the visual system demonstrated that electrical activity plays a critical role in the refinement of neural circuits[19-22]. Axons from the left and right eye project to the lateral geniculate nucleus (LGN) of the thalamus[23]. The thalamus sends projections to the visual, or striate, cortex, relaying information from the eyes[23]. In the mature nervous system, inputs from each eye are segregated into distinct segments in the LGN and cortex[23]. The compartments in the visual cortex, termed ocular dominance columns, were identified by the striped patterns seen on cortical sections after injecting dye into one eye[19-23]. In a classical experimental paradigm, vision was occluded in one eye of a developing cat[19,22]. Even when monocular occlusion was restricted to a short window of time, a loss of ocular dominance columns was observed in the visual cortex[19-24]. Additionally, the presynaptic arbors of the axons from the occluded eye were much smaller, whereas arbors from the non-deprived eye expanded[25-26]. Later studies found that the ocular dominance columns form before birth but can be lost during postnatal critical periods if circuit activity is interrupted[27]. Extensive refinement also occurs at the LGN[2]. The cells of the LGN are initially innervated by multiple retinal axons, but following eye opening, these synapses are eliminated so that only 1-3 inputs remain[2,23].

Similarly, a critical role for circuit activity at the vertebrate NMJ has been well characterized[28-29]. The NMJ consists of the presynaptic motor neuron and the postsynaptic muscle fiber, ensheathed by a Schwann cell[30]. The presynaptic neuron releases acetylcholine (ACh), which binds to postsynaptic ACh receptors located on the membrane of the muscle fiber[30]. Initially, multiple axons from different motor neurons synapse with the same muscle fiber[23]. Excess inputs are eliminated over time, resulting in each muscle stabilizing innervation from only one motor neuron (**Figure 1**)[31-32]. During the elimination process, one input becomes stronger, whereas the other axons become weaker and retract[15]. Studies show that blocking activity results in defective elimination and increased numbers of inputs[15,28-29,31]. Additionally, higher levels of activity can induce input elimination in less time[15,31-33]. It appears that both presynaptic and postsynaptic activity play an important role in circuit refinement[15,31,35]. Studies of the rodent NMJ have demonstrated that modulating activity in the axon or muscle cell can influence synaptic elimination[15,34-35].

Data now suggest that activity may not be sufficient to promote input elimination; rather, it is proposed that the pattern of neuronal firing dictates synapse refinement. Mature motor neurons that innervate the same muscle fire asynchronously[36-37]. Interestingly, *in vitro* studies of the mammalian NMJ show that activity is synchronous early in development, prior to synapse refinement[36-37]. During development, synchronous activity is replaced by

asynchronous firing, and this occurs around the onset of input elimination[36-37]. The imposition of synchronous activity on the NMJ inhibits the input elimination[36-37]. This study suggests that differential activity is needed at the NMJ to stabilize the active synapses and to prune the less active inputs. Additionally, visual system refinement is sensitive to the pattern of activity. Studies show that flashing strobe lights into the eyes of goldfish and frogs during the critical period of visual circuitry refinement delays synapse elimination and thus fails to maintain ocular dominance columns[38-39]. These results correlate with the Hebbian paradigm in which neurons that fire together are strengthened and maintained, whereas noncoincident activity weakens connections[40-42].

Taken together, these studies demonstrate that patterned circuit activity is a conserved player in remodeling the nervous system. Interestingly, not all synaptic refinement events are modulated by activity. Hormonal signaling controls metamorphosis in insects, whereas axon guidance molecules can mediate retraction in the vertebrate CNS[17,43]. Additionally, refinement can occur at electrically silenced NMJ synapses *in vitro*[44]. These results are important because they show that both activity-dependent and independent pathways can modulate synaptic remodeling.

Competition at the Vertebrate Neuromuscular Junction

Studies at the vertebrate NMJ have been critical in demonstrating that multiple synaptic inputs compete with one another to innervate a target muscle fiber[25,31,45]. *In vitro* studies showed that in muscle fibers that are innervated by two motor neurons, stimulation of one neuron led to suppression of inputs from the other neuron[35]. The mechanism of this effect was explored *in vivo* by genetic ablation of choline acetyl-transferase (ChAT) in a subset of motor neurons, thus selectively depleting biosynthesis of the neurotransmitter acetylcholine[31]. When competing with wild-type neural inputs, the ChAT-depleted inputs lost the competition to innervate[31]. This study demonstrates that more active inputs out-compete weaker inputs to stabilize innervations with target muscle. One motor neuron may lose innervation at one site but out-compete and stabilize connections at other sites, suggesting a mechanism to bias connections for maintenance or removal[46]. Interestingly, the competition of motor neurons is reversible[45,47-48]. Increasing the activity in weaker inputs can cause initially "losing" motor neurons to "win" the competition[45]. Recent studies demonstrate that axons undergoing elimination will reverse their fate if the innervating axon is excised[45]. This finding suggests that the pruning process is not all-or-none but rather is a continually driven process[30]. Another interesting characteristic of elimination is that at no time in the refinement process are muscle fibers without innervation, indicating that cellular mechanisms may exist to detect synaptic density and ensure all muscle fibers maintain input from at least one motor neuron[49].

Studies of competition at the vertebrate NMJ have led to the idea that axons may be competing for a limited trophic factor released from the post-synaptic muscle[4,15,30]. The inputs with access to more trophic factor are stabilized, whereas inputs receiving less trophic factor are eliminated[15]. Studies show that trophic support is required for the maintenance of synapses[50]. The loss of the neurotrophin-4 ligand or its receptor TrkB promotes synaptic elimination at the muscle and cerebellum[51-52]. Overexpression of neurotrophin-4/5 and brain derived neurotrophic factor (BDNF), ligands of the TrkB receptor, prevent elimination and promote synapse stabilization in the visual circuitry of cats[53-54]. Additionally, studies at the NMJ suggest that the postsynaptic muscle must have a mechanism to communicate with the presynaptic motor neurons; however, this signal has not yet been identified[15]. It remains speculative that neurotrophins are the retrograde signal at the NMJ that stabilize a single motor neuron while destabilizing others. Taken together, these studies suggest that the local control of trophic factors may contribute to the stabilization or removal of competing axons.

It is important to note that not all synapse elimination events involve competition between multiple inputs. At the *Drosophila* NMJ, motor neurons innervate target muscle without competing against other inputs; however, the size of the synapses increases greatly over time[55]. In coordination with this synaptic growth, disassembly occurs in restricted areas and the postsynaptic muscle expands[30,55-56]. Additionally, competition between inputs does not appear to dictate synapse disassembly in the refinement of *C. elegans* GABAergic circuitry although this process is activity-dependent[9,57]. These results imply that competition between inputs may be characteristic of the more complex vertebrate nervous systems, while activity-dependent refinement is conserved in simpler invertebrate neural circuits.

Uncovering the Molecular Mechanisms of Synaptic Disassembly

It is unclear what molecular mechanisms connect activity in the nervous system to the cellular constituents that

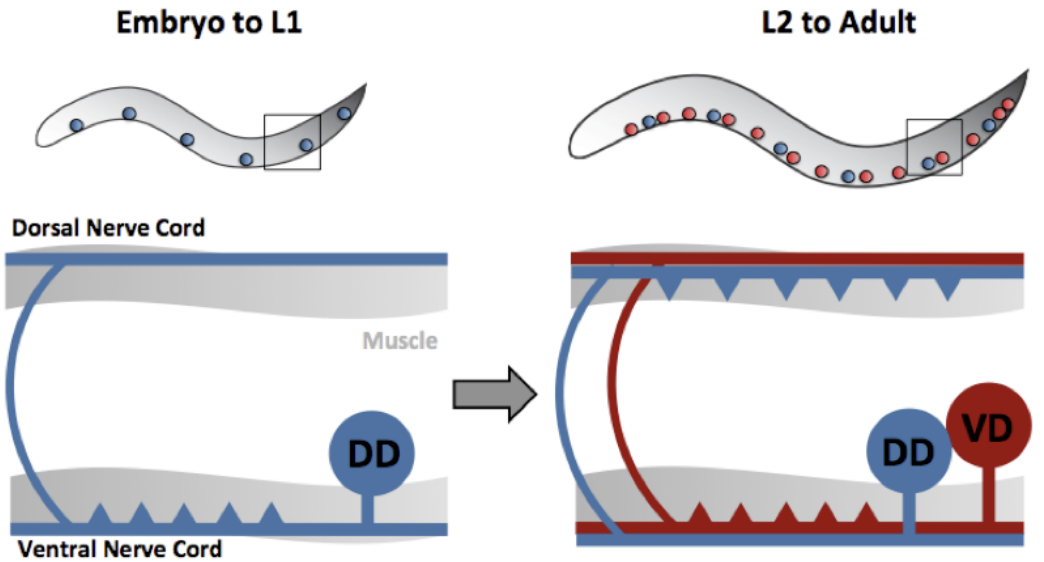

Figure 2: *Remodeling the GABAergic motor circuit in C. elegans.* Dorsal D (DD) motor neurons initially innervate ventral muscle (blue triangles), then relocate these synapses to dorsal muscles following the first larval stage (L1). The Ventral D (VD) motor neurons are generated in the second larval stage (L2) and synapse with ventral muscles (red triangles).

physically dismantle synapses. One hypothesis involves the activity-dependent destabilization of synapses by the ubiquitin proteasome system (UPS)[58-63]. The proteasome regulates protein concentrations in the cell and removes defective proteins by degradation[62]. Proteins are targeted for proteasomal destruction by ubiquitin molecules[62]. This process involves three enzymes: the ubiquitin-activating enzyme (E1), the ubiquitin-conjugating enzyme (E2), and the ubiquitin ligase (E3)[62]. The E3 ubiquitin ligase is responsible for substrate specificity[62]. Studies show that ubiquitination of both pre- and post-synaptic proteins occur at the synapse[58-63]. Interestingly, the ubiquitination of proteins at the synapse also appears to be modulated by activity[59-60]. A study in isolated vertebrate hippocampal neurons shows that in response to activity, the UPS degrades PSD-95, a scaffolding protein in the postsynaptic cell[58]. Activity-induced ubiquitination of PSD-95 induces the internalization of AMPA receptors. Thus, this study connects circuit activity to protein turnover and molecular changes at the synapse[58]. Another study shows that Shank, GKAP and AKAP79/150 postsynaptic scaffolds selectively undergo activity-dependent ubiquitination[59]. The selective ubiquitination of scaffolding proteins and their associated proteins could be a mechanism to regulate synapse stability in response to activity[59]. Additionally, it was found that during synapse removal, distinct scaffolds of proteins are eliminated at different times, showing that differential regulation of groups of proteins play an important role in the process of disassembly[64].

Examining the activity-dependent ubiquitination of presynaptic proteins has led to similar findings[60-61]. Studies at the *Drosophila* NMJ show that proteasome inhibitors strengthen synaptic transmission through up-regulation of a vesicular priming component DUNC-13[60]. An additional study in *C. elegans* proposes an interesting model for protecting synapses from ubiquitination and destruction[61,65]. The immunoglobulin protein SYG-1 interacts with the E3 ubiquitin ligase SKR-1[61]. This interaction blocks the binding of SKR-1 to adaptor protein SEL-10, needed for ubiquitin-mediated target selection, thus blocking presynaptic ubiquitination in this area of the neuron[61]. This study also suggests that in different areas of the same axon that lack SYG-1, SKR-1 is free to join the active ubiquitin complex and dismantle synapses[61]. This model introduces a mechanism by which the presynaptic neuron can spatially dictate synaptic stabilization along a single axon[61]. Taken together, these studies demonstrate that ubiquitination of pre- and post-synaptic components may act as a mechanism connecting activity to the cellular processes that destabilize the synapse. More studies will be necessary to understand what specific proteins are targeted for degradation in these systems and how the loss of targeted proteins affects synaptic stability.

Circuit Remodeling in *C. elegans*: A Model of Synaptic Removal

While the examination of vertebrate systems has been helpful to our understanding of synaptic remodeling, it is becoming more apparent that refinement is complex and

COUP-TFII: (chicken ovalbumin upstream promoter transcription factor-2) highly conserved transcription factor involved in patterning the nervous system in addition to controlling development of multiple organs in the body.

may involve the coordination of multiple cellular processes. Therefore, there is a demand for a simplified model to examine how different conserved pathways are acting with one another to regulate such a complex event. The nematode *C. elegans* is widely used for its ease of genetic manipulations and its highly conserved genome. Interestingly, a subset of neurons in the worm undergoes expansive remodeling during development[9]. The GABAergic Dorsal D (DD) motor neurons are born embryonically and make synapses onto ventral muscles[9]. At a critical window of development, specifically between the first (L1) and second (L2) larval stages, DD synapses with ventral muscles are removed as new DD connections are established with dorsal muscles[9]. Coincidentally, Ventral D's (VDs) are born and innervate the ventral muscle (**Figure 2**)[9]. The UNC-55/COUP-TFII transcription factor functions in VDs to inhibit remodeling [66-67]. When UNC-55 is genetically ablated, the VDs ectopically remodel, and conversely, over-expression of UNC-55 in DDs blocks remodeling[66-68]. Therefore, the UNC-55 transcription factor is necessary and sufficient to inhibit the GABAergic motor neuron remodeling program. Activity in the form of neurotransmitter release also modulates this process. Mutants that decrease synaptic vesicle fusion show delayed DD remodeling, whereas mutants that increase neurotransmitter release demonstrate precocious or early remodeling[69]. Recent work demonstrates that this process is very complex. A microarray study was performed to uncover the targets of UNC-55, with the assumption that these would be candidate synaptic remodeling genes[18]. This approach identified 49 candidate genes with gene ontology categories ranging from ubiquitin regulation, calcium binding proteins, ion channels, enzymes, extracellular matrix components, transcription factors, cytoskeletal components, and proteins involved in neurotransmission[18]. This study demonstrates the complex nature of the remodeling process and yields candidate genes that may be conserved in refinement of the mammalian central nervous system.

Conclusions

The regulation of synaptic refinement is complex; however, with the use of model organisms we are developing deeper insight into the molecular mechanisms that govern this form of neural plasticity. Despite the complexity of the mammalian central nervous system, we have seen that synaptic refinement relies on the activity of neural circuitry and is characterized by competition between multiple inputs. Additionally, it appears that mechanisms to destabilize the synapse may play a role in activity-dependent synapse disassembly. It is unclear how the nervous system is able to coordinate the assembly, disassembly, and reassembly of a vast number of synapses during development. This suggests that the nervous system requires mechanisms to control synapse formation and retraction, in addition to mechanisms that balance the two. Much work will be necessary to elucidate the molecular constituents that refine functional neural circuitry. The utilization of model organisms with simplified nervous systems and malleable genetics will be of great value in exploring these intriguing questions.

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