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Development of Fast Neurotransmitter Synapses: General principle and Recent progress

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In the mammalian central nervous system (CNS), chemical synapses are specialized intercellular apparatuses that mostly form during early postnatal development and mediate rapid communication among neurons. Accumulating evidence has shown that synapse formation is a multi-step process with initial steps involving trans-synaptic interactions of cell adhesion molecules that trigger accumulation of the essential components at both presynaptic and postsynaptic sites [4, 11, 12, 14, 16, 19]. Nascent synapses generally undergo a highly-regulated selection process that involves complex signaling events including synapse validation, retention or even elimination. Finally, a portion of nascent synapses mature through an activity or experience-dependent refinement process to become functional.

Development of excitatory glutamatergic synapses and inhibitory GABAergic/glycinergic synapses largely involve different processes but that nevertheless share apparent commonalities. For example, while the vast majority of glutamatergic synapses at pyramidal neurons are formed on dendritic spines, GABAergic synapses are developed independent of dendritic protrusions. In developing neurons, dendritic filopodia, the precursor of spines, actively search for nearby glutamatergic axons to make initial contacts [5, 8, 22, 23]. In contrast, newly formed GABAergic synapses in hippocampus exclusively form at pre-existing axon-dendrite crossings [21]. These observations suggest that development of GABAergic synapses involves mechanisms distinct from that of glutamatergic synapses. Nevertheless, convincing evidence has demonstrated that cell adhesion molecules are critical for both excitatory and inhibitory synapse development, suggesting that trans-synaptic interactions are a common requirement for the formation of different types of synapses [4, 6, 10, 12]. Interestingly, distinct sets of cell adhesion molecules are enriched at excitatory vs inhibitory synapses [4, 6, 10, 12], suggesting different synaptogenic machineries present at these synapses to instruct their formation respectively.

Dysregulations of synapse development can lead to neurodevelopmental and psychiatric disorders such as autism spectrum disorders (ASDs) [24]. Indeed, many rare mutations in

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cell adhesion molecules have been associated with ASDs [17, 24]. Autistic patients and animal models of autism have deficits in both excitatory and inhibitory synapse development [24]. Thus, understanding molecular and cellular mechanisms underlying synapse development will not only shed light on how neural circuit is assembled in the normal brain, but also provide important insights into pathogenesis of many brain illnesses.

In this Special Issue, neuroscientists working in synapse development and related fields discuss formation and regulation of chemical synapses in the brain. For excitatory glutamatergic synapses, **Parajuli et al.,** [13] provide a systematic review on the formation, function, molecular composition and stability of nascent spines. Using Purkinje cells (PCs) as a model to study synaptogenesis and synaptic specificity, **Sassoe-Pognettoet al.,** [15] discuss molecular mechanisms underlying the domain-specific formation of synaptic connection. **Lu and Zuo** [9] highlight the functional implication of clustered spine plasticity, rather than random spine formation along dendrites, as an activity dependent mechanism for plasticity. **Chen and Geng** [3] review recent exciting progress of synapse engineering to manipulate synapses that allows more precise manipulation of synapses in behaving animals.

For inhibitory synapses development, **Lu et al.,** [10] discuss the key role of postsynaptic transmembrane molecules in the development of GABAergic inhibitory synapses, including NMDA receptors, $GABA_A$ receptors, synaptogenic cell adhesion molecules and immunoglobulin superfamily proteins. **Wierenga** [20] highlights the importance of local exchange of synaptic adhesion molecules, actin dynamics and activity-driven fine-tuning in GABAergic presynaptic development. **Alvarez** [1] provides a comprehensive review of the development and regulation of glycinergic synapses with a focus on scaffolding protein gephyrin.

In addition, two reviews discuss the role of glial cells in the regulation of formation, elimination and function of chemical synapses. **Krencik et al.,** [7] review how human astrocytes contribute to circuit formation with a focus on unique features of human astrocytes that may be important contributors to high functional capacity of human brain. **Terni et al.,** [18] discuss the role of glial cells in synapse elimination during development and emphasize the importance of glia and neuron coordination in the refinement of synaptic connectivity.

Dysregulation of synapse development can lead to devastating brain disorders. **Baig et al.,** [2] summarize genetic variants and rare mutations of cell adhesion molecules as risk factors for ASDs and discuss molecular mechanisms for their etiology.

In summary, the compilation of reviews in this Special Issue provide a rich view of the molecular mechanisms that underlie synapse formation and maturation, and they underscore the commonalities and differences in the mechanisms that regulate excitatory and inhibitory synapse development.

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