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Susumu Tomita is a professor of Cellular and Molecular Physiology and Neuroscience, primary member of Program in Cellular Neuroscience, Neurodegeneration and Repair (CNNR) and the Kavli Institute for Neuroscience, Yale University School of Medicine. Tomita laboratory aims to discover and engineer molecular machineries to control synaptic transmission and plasticity. Our approach is identifying molecules that determine number and properties of individual neurotransmitter receptors at synapses, followed by co-reconstituting such molecules with neurotransmitter receptors to faithfully reconstruct synaptic transmission. We have identified molecular constituents of neurotransmitter receptors including their auxiliary subunits and discover machineries for synaptic plasticity.

Neurons have the formidable task of generating action potentials to represent information from the external world, reflect the status of an animal's internal state, and generate meaningful behaviors that connect the two. The action potential, however, is only the exclamation mark at the end of a nuanced and dynamic conversation between a neuron and it's thousands of synaptically connected partners. The rules of engagement for synaptic connections become the syntax of a circuit, built from the molecules that regulate synapse formation, function, and plasticity. Never is this more apparent than when seeking to understand and treat disorders of the brain. Dysregulation of synaptic proteins and the extensive cell biology that supports synapse function is a recurrent theme that emerges from studies of neurodevelopmental, psychiatric, and neurodegenerative disorders. The most promising avenues for therapies organically grow from the identification and investigation of relevant molecules.

In this volume of Current Opinion in Neurobiology, we hope to draw your attention to some of the most recent, often surprising, and occasionally controversial advances in our understanding of the molecular basis of synapse function. Through the use of new tools, methods, and technologies there is increasing experimental dexterity that is being applied to the study of synapses. As a result, there is growing fluidity between our understandings of molecules, the molecular networks they operate within, the specific cell types and conditions under which they are produced, and how they impact synapses, circuits, and ultimately behavior. In this issue, investigators at the vanguard of molecular neuroscience have shared highlights of this progress and inspire new directions for pushing the field forward is pursuit of understanding the molecular life of the synapse.

Early in development and throughout the life of an animal, new synapses need to be formed, modulated, and in some cases eliminated. Even when synapse formation occurs en masse, connectivity needs to be established between the right partners. Baldwin and Eroglu described recent advances in our understanding of how glial cells regulate synaptogenesis through the secretion of proteins, lipids, and small molecules. They highlight some of the remarkable specificity of this biology: within a circuit, molecules secreted by glia prove to be synaptogenic only for synapses made between certain presynaptic and postsynaptic neurons. Presynaptic and postsynaptic neurons also use a variety of secreted, transmembrane, and cell adhesion molecules to inform their choice of synaptic partners and recruit the appropriate neurotransmitter receptors to the synapse. Members of the C1q family of proteins (Cbln1 and C1qls), discussed by Yuzaki, are secreted by presynaptic neurons and regulate synapse formation and postsynaptic organization through their interaction with postsynaptic neurotransmitter

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Brenda Bloodgood is an assistant professor in the Division of Biological Sciences, Neurobiology section at UC San Diego and a Faculty Fellow in the Kavli Institute for Brain and Mind. Dr. Bloodgood's research explores the molecular mechanisms that guide experience-dependent plasticity of neural circuits. Work from her lab ranges from the dissection of signaling pathways confined to subcellular compartments to gene regulatory networks that define how populations of neurons are connected. These studies are uncovering new strategies used by neurons for communicating the dynamics of ongoing circuit activity to the nucleus and the exquisite precision through which activity-regulated gene expression regulates synaptic connectivity.

receptors or GPCRs. Williams and colleagues dive into how growth factors (FGFs), an endocannabinoid synthesizing enzyme (DGLα), and a member of the IgG superfamily of proteins (Kirrel3), build and modulate specific excitatory and inhibitory synaptic connections in the hippocampus.

Interactions among neurons are mediated by a dizzying array of cell adhesion molecules. Zinn and Özkan share recent progress in understanding this interactome, highlighting interaction networks formed by several subfamilies of immunoglobulin cell adhesion molecules. Roche and colleagues discuss the importance of posttranslational modifications of neuroligins, cell adhesion molecules well known for their role in synapse regulation and in neuro-glial signaling. Kim and colleagues describe synaptic adhesion molecules, their downstream signaling and how they converge on major excitatory neurotransmitter receptors, that is, glutamate receptors. Turning to the molecular machinery at inhibitory synapses, Brose and colleagues review our bourgeoning understanding of inhibitory synapse cell adhesion molecules and the interactions with GABA and glycine receptors.

This naturally brings us to the extraordinary complexity of postsynaptic terminals — both excitatory and inhibitory. Since molecular cloning of neurotransmitter receptors 30 years ago, the focus has largely been on the receptors themselves. However recently, receptor complexes are being more articulately described and it is clear that the constituents of these native complexes play critical roles in shaping synapse function. Proteomic approaches allow the field to analyze protein complexes systematically, and with less bias and greater sensitivity. Fakler and Bettler review advanced proteomic analyses of neurotransmitter complexes, specifically those containing ionotropic AMPA receptors and metabotropic GABA-B receptors. From this synthesis they described functional roles for constituents of the receptor complex. Jacobi and von Engelhardt discuss diversity in native AMPAR complexes, and their unique and various functions. This information is particularly relevant as the biomedical community tries to understand heterogeneity in synaptic responses and the implications for the development of therapeutic interventions that target excitatory synapses. Frank and Grant provide an overview of the web of protein interactions within the postsynaptic density by highlighting supercomplexes of NMDAR receptors and MAGUKs. The authors introduce a hierarchical framework of signaling beginning with receptor complexes, moving to protein–protein supercomplexes, and terminating in a postsynaptic nanodomain.

Postsynaptic terminals are broadly categorized as excitatory or inhibitory based on the ionotropic receptors they contain. Presynaptic terminals are proving to be less amenable to this simple parcellation. Many neurons are now recognized to release multiple neurotransmitters, possibly from the same terminals and vesicles. Sabatini and colleagues describe four types of multi-transmitter neurons and discuss the functional implications of these mixed messages — including how co-release muddles interpretations of the already challenging connectomic wiring diagrams. Neurotransmission of any sort is immensely expensive energetically. Ryan and Ashrafi discuss the sophisticated regulation of glycolysis in synaptic terminals and how dysregulation of metabolism in this particular subcellular compartment may contribute to neurodegeneration.

The flexibility of synapse function allows a neuron to change the likelihood that a given set of inputs will drive it to spike. Protein modifications within synapses and structural changes of the spines that enclose them play fundamental roles. Globa and Bamji review the growing list of palmitoylated