Key Determinants of Synaptic Excitation/Inhibition Imbalance in Autism Spectrum Disorders - From Genetic Animal Models to Human Patients, (SynPathy)

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Nerve cells in the brain communicate via specialized contacts called synapses, and information processing in the brain critically depends on a proper balance between stimulatory (excitatory) and inhibitory signaling at synapses (E/I balance). Mutations in genes that determine synapse function and E/I imbalances are observed in many brain disorders, including autism spectrum disorders (ASDs) and schizophrenia, which led to the notion that they are - at least in part - disorders of synaptic connectivity or 'synaptopathies'. Fascinatingly, neuronal networks in the brain typically maintain an exquisite E/I balance although neural activity varies constantly, but the molecular and cellular mechanisms that allow neurons to maintain stable E/I ratios are largely unknown. Synaptic adhesion molecules, which connect neurons at synapses and regulate excitatory and inhibitory synapse formation and function, are thought to be major players in tuning E/I balance. However, how different synaptic adhesion molecules regulate the recruitment of the elements of the synaptic machinery needed to adjust E/I ratios is entirely unclear. **We aim to unravel key molecular mechanisms that control E/I balance in the brain.** Specifically, we propose that the interplay between two classes of surface proteins that have opposing functions and were both shown to be involved in ASD and schizophrenia - MDGAs and NLGNs - tunes E/I balance. We propose (i) that the interaction between the synapse developmentsuppressing
MDGA proteins and the synapse development-promoting NLGN proteins precisely
controls the function of key synaptic adhesion molecules, the recruitment of synaptic neurotransmitter receptors, and the local synaptic protein synthesis machinery, and (ii) that perturbations of these processes lead to E/I imbalances and, consequently, to neurodevelopmental disorders such as ASDs and schizophrenia. To test these hypotheses, we will study novel genetic mouse models that model human disorders and patient-derived neurons. With our focus on two classes of proteins involved in ASDs and schizophrenia, combined with the use of highly sophisticated experimental models and the synergistic expertise of the partners, we expect to be able to determine key disease mechanisms and to provide important leads for diagnostic and therapeutic approaches.