

Phase Separation at the Nerve Terminal

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Neuronal transmission relies on the sustained release of neurotransmitters from synaptic vesicles (SVs) upon depolarization of neurons. Nerve terminals contain hundreds of SVs that form tight clusters. Despite being held together, vesicles are highly mobile within these clusters, so that they can be randomly recruited to the surface of the cell to release their content upon activation of the neuron. How this compact, yet the dynamic organization is achieved remained elusive. Several studies in the past decade showed that macromolecules may assemble into distinct liquid compartments not-limited by a membrane, a process known as liquid-liquid phase separation.

Recently we have discussed (Milovanovic and De Camilli, *Neuron*, 2017) how several features of SV clusters suggest that they may be part of a distinct liquid phase in the cytosol. For example, SV clusters have sharp boundaries, exclude other organelles, vesicles in these clusters are mobile, and SVs can be exchanged with vesicles outside the cluster. Thus, SV cluster may represent a distinct liquid phase in which one component of the phase are synaptic vesicles and the other component are proteins of the intervening matrix.

In our latest study (Milovanovic et al., *Science*, 2018), we show that synapsin 1, a highly abundant synaptic protein, forms a distinct liquid phase in an aqueous environment. Synapsin 1 exchanges readily between the phase where is enriched and the surrounding medium. Additional synapsin 1 binding scaffolding proteins further modulate this phase but are not necessary for its formation. Importantly, synapsin 1 can capture small lipid vesicles into its phase. The phase of synapsin 1 rapidly disassembles upon phosphorylation by CaMKII, mimicking the dispersion of synapsin 1 that occurs at presynaptic boutons upon simulation. Thus, a minimal system of synapsin (with or without its binding partners) may sequester lipid vesicles, forming a distinct liquid phase.