Report

Neuron

Topographic Mapping of the Synaptic Cleft into Adhesive Nanodomains

Highlights

- A macromolecular definition is given for synaptic cleft organization
- SynCAM 1 shapes the cleft edge, while EphB2 is enriched deeper postsynaptically
- *Trans*-synaptic complexes can assemble into cloud-like ensembles at the synaptic edge
- Synaptic adhesion complexes undergo dynamic, activity-dependent redistribution

Authors

Karen Perez de Arce, Nikolas Schrod, Sarah W.R. Metzbower, ..., Thomas A. Blanpied, Vladan Lučić, Thomas Biederer

Correspondence

thomas.biederer@tufts.edu

In Brief

Perez de Arce et al. show that the cleft of excitatory synapses is composed of structurally and molecularly defined sub-compartments, the cleft is dynamic, and *trans*-synaptic interactions shape the cleft's edge. These findings bring the concept of nanodomains to the cleft.

Perez de Arce et al., 2015, Neuron *88*, 1165–1172
December 16, 2015
http://dx.doi.org/10.1016/j.neuron.2015.11.011

CellPress

Neuron
Report

Topographic Mapping of the Synaptic Cleft into Adhesive Nanodomains

Karen Perez de Arce,[1] Nikolas Schrod,[2] Sarah W.R. Metzbower,[3] Edward Allgeyer,[4] Geoffrey K.-W. Kong,[2,6] Ai-Hui Tang,[3] Alexander J. Krupp,[5] Valentin Stein,[5] Xinran Liu,[4] Jörg Bewersdorf,[4] Thomas A. Blanpied,[3] Vladan Lučić,[2] and Thomas Biederer[1,*]

[1]Department of Neuroscience, Tufts University School of Medicine, Boston, MA 02111, USA
[2]Department of Molecular Structural Biology, Max Planck Institute of Biochemistry, 82152 Martinsried, Germany
[3]Department of Physiology, University of Maryland School of Medicine, Baltimore, MD 21201, USA
[4]Department of Cell Biology, Yale University School of Medicine, New Haven, CT 06520, USA
[5]Department of Physiology, Universität Bonn Medical Faculty, 53115 Bonn, Germany
[6]Present address: Plant Molecular Biology Laboratory, University of Hong Kong, Hong Kong, PRC
*Correspondence: thomas.biederer@tufts.edu
http://dx.doi.org/10.1016/j.neuron.2015.11.011

SUMMARY

The cleft is an integral part of synapses, yet its macromolecular organization remains unclear. We show here that the cleft of excitatory synapses exhibits a distinct density profile as measured by cryo-electron tomography (cryo-ET). Aiming for molecular insights, we analyzed the synapse-organizing proteins Synaptic Cell Adhesion Molecule 1 (SynCAM 1) and EphB2. Cryo-ET of SynCAM 1 knockout and overexpressor synapses showed that this immunoglobulin protein shapes the cleft's edge. SynCAM 1 delineates the postsynaptic perimeter as determined by immunoelectron microscopy and super-resolution imaging. In contrast, the EphB2 receptor tyrosine kinase is enriched deeper within the postsynaptic area. Unexpectedly, SynCAM 1 can form ensembles proximal to postsynaptic densities, and synapses containing these ensembles were larger. Postsynaptic SynCAM 1 surface puncta were not static but became enlarged after a long-term depression paradigm. These results support that the synaptic cleft is organized on a nanoscale into sub-compartments marked by distinct *trans*-synaptic complexes.

INTRODUCTION

Neuronal transmission requires precise organization of pre- and postsynaptic specializations (Harris and Weinberg, 2012; Sigrist and Sabatini, 2012). Limited structural insights are available into the synaptic cleft, the third compartment of a synapse. Current results show that the complexes spanning the cleft form net-like structures that can be periodically arranged (Lučić et al., 2005; Zuber et al., 2005; High et al., 2015).

Trans-synaptic interactions modulate synapse development and plasticity (Missler et al., 2012). Ultrastructural localization of N-cadherin shows that it is expressed throughout the cleft of developing synapses and present at the edge of mature synapses (Elste and Benson, 2006; Uchida et al., 1996; Yamagata et al., 1995). N-cadherin does not induce synapses, and comparable insights into synaptogenic proteins are lacking, though immunoelectron microscopy (immuno-EM) studies have demonstrated the differential expression of neuroligins at excitatory and inhibitory synapses (Song et al., 1999; Varoqueaux et al., 2004; Mortillo et al., 2012). Synaptogenic proteins may demarcate and function at specialized synaptic zones, yet limited understanding of cleft topography restricts addressing these questions.

We here delineated macromolecular properties of the excitatory synaptic cleft. To gain molecular insights, we investigated two proteins that form *trans*-synaptic complexes to promote excitatory synapse number, the immunoglobulin adhesion protein SynCAM 1 (Synaptic Cell Adhesion Molecule 1, also named nectin-like 2 or Cadm1) (Biederer et al., 2002; Fogel et al., 2007; Robbins et al., 2010) and the EphB2 receptor tyrosine kinase (Sheffler-Collins and Dalva, 2012). Analysis of excitatory synapses by cryoelectron tomography (cryo-ET), immuno-EM, and STED (stimulated emission depletion) and STORM (stochastic optical reconstruction microscopy) super-resolution imaging supports that the synaptic cleft is composed of structurally and molecularly defined sub-compartments.

RESULTS

Structural Organization of the Cleft of Excitatory Synapses

Cryo-ET enables high-resolution imaging of the entire cleft in a fully hydrated, physiologically relevant state (Lučič et al., 2013). We recorded tomograms of neocortical synaptosomes from adult mice (Figures 1A and S1A). All analyzed synapses were asymmetric with a postsynaptic density (PSD) and likely corresponded to excitatory synapses. The mean cleft width of wild-type (WT) synapses was 22.0 ± 0.5 nm (Figure S1C), as described (Rees et al., 1976). Numerous complexes spanned the cleft and often assumed the shape of a laterally extended, net-like density (Figure 1A; Movie S1), as described (Lučić