MULTI-COLOR STORM IN NEURONS REVEALS MOLECULAR ORGANIZATION OF THE LGI1 SYNAPTIC COMPLEX

Lara Laparra-Cuervo[1], Laurent Ladépêche[1,2], Jesús Planagumà[1,2], Joseph S. Borbely[3], Ángel Sandoval[1], Josep Dalmau[2,4,5], Melike Lakadamyali[1]

[1]ICFO-Institut de Ciències Fotòniques, The Barcelona Institute of Science and Technology
Av. Carl Friedrich Gauss, num. 3
08860 Castelldefels (Barcelona), SPAIN
[2]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, Universitat de Barcelona, Barcelona, SPAIN
[3]Measurement Standards Laboratory, Lower Hut, NEW ZEALAND
[4]Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA
[5]Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, SPAIN

E-mail: lara.laparra@icfo.eu

KEY WORDS: multicolor STORM, super-resolution imaging, neurons, LGI1

LGI1 autoimmune encephalitis is a severe neuropsychiatric disorder related to epilepsy. It is an antibody-mediated pathogenesis where the patients produce autoantibodies against leucine rich glioma activated 1 (LGI1), which alter synaptic plasticity. However, the molecular mechanisms that lead to the observed problems in patients still remain largely unknown.

LGI1 is a secreted protein that forms a trans-synaptic bridge linking pre- and post-synaptic transmembrane proteins (ADAM22 and ADAM23) and helps to organize a multimeric complex at the synapse including AMPAR and voltage-gated potassium channels [1]. Yet, the molecular architecture of the LGI 1 complex has not been directly visualized due to the small length scale and the crowded environment of the synapse. This molecular architecture is highly important for maintaining neuronal homeostasis and is likely disrupted by autoantibodies during LGI 1 encephalitis.

By means of multi-color STORM [2], we have visualized the synaptic organization of the different proteins and receptors directly or closely involved in LGI1 functioning at the nanoscale level. Using well-characterized synaptic markers (Homer and Bassoon) as molecular standards, we have determined the positioning of LGI1 and 4 other related proteins (AMPAR, ADAMs and voltage-gated potassium channels) within the synaptic space at nanoscale resolution in 3-color STORM images. Comparing this molecular architecture in healthy versus diseased neurons will give important insights into how the LGI1 antibodies may alter synaptic localization and stoichiometry of the LGI1 macromolecular complex leading to loss of synaptic homeostasis.

[1] Lancaster et al., "Encephalitis and antibodies to synaptic and neuronal cell surface proteins", *Neurology*, *77*, 179-189, 2011
[2] Dani et al., "Superresolution Imaging of Chemical Synapses in the Brain", *Neuron*, 68, 843–856, 2010