Function of BAD-LAMP in the CNS

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Role of Bad-LAMP in brain development and function

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BAD-LAMP

We identified a new membrane protein, BAD-LAMP (for Brain and Dendritic cell specific Lysosome Associated Membrane Protein). BAD-LAMP shows strong homoglogy to UNC-46, a protein that positively interacts with the vesicular GABA transporter UNC-47 in C. elegans. In mice, its expression is correlated with terminal neuronal differentiation and synaptogenesis in the developing and postnatal nervous system. We investigated the function of BAD-LAMP in this project using cell biological and mouse genetics approaches.

Cell biology of BAD-LAMP

Based on structural homologies with the UNC-47 molecule, which is the vesicular GABA transporter and has been shown to interact with BAD-LAMP/UNC 46 in *C. elegans,* we hypothesized that BAD-LAMP could also interact with the multiple membrane spanning domains protein UNC-93B1. Interestingly, when BAD-LAMP and UNC93B1 are ectopically expressed together in HeLa cells, they mutually influence their intracellular localization and efficiently co-localize to a specific subset of late endosomes. Thus BAD-LAMP seems to be part of a specialized molecular complex chaperoning UNC93B1 and represents a novel marker of human primary and transformed pDCs, since it is also expressed in blastic plasmacytoid dendritic cell neoplasm (BPDCN).

BAD-LAMP at the synapse

As mentioned above, data in C. elegans pointed towards a role of BAD-LAMP in GABA neurotransmitter signaling. In agreement, BAD-LAMP antibodies showed specific immunoreactivity in the external plexiform layer of the OB where GABAergic olfactory interneurons synapse to olfactory projection neurons and in the globus pallidus and the reticular part of the Substantia Nigra that are both direct targets of the GABAergic striatal neurons.

Moreover, immunohistochemistry and EM showed that Bad-Lamp is specifically expressed at GABAergic synapses. This is exemplified by co-localization of the protein with VIAAT, the vesicular inhibitory amino acid transporter in the olfactory bulb external plexiform layer (Fig. 1a arrows). High resolution imaging using EM demonstrated that within interneuron spines, BadLamp is always found in the clouds of synaptic vesicles in proximity to the membrane densities that represent synaptic sites (Fig. 1b, arrowhead). In conclusion, this part of the work strongly indicates a role of BadLamp in synaptic function. This is of outstanding importance in the light of the recent description that C. elegans orthologue of BadLamp, UNC 46, is a chaperone like molecule, necessary for the insertion/activation, in synaptic vesicles, of the neurotransmitter transporter UNC-47, the C. elegans ortholog of VIAAT.

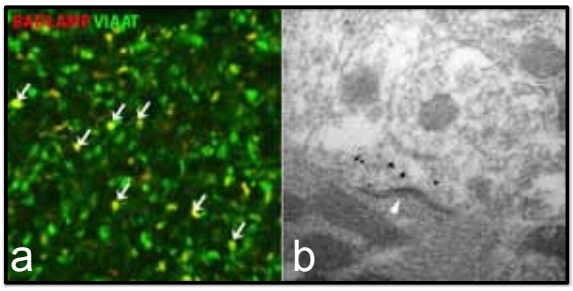

Figure 1: Immunofluorescent (a) and electron microscopy (b) immunohistochemistry in the external plexiformm layer of th olfactory bulb.(a) BAD-LAMP immunoreactivity (IR) co-localizes with VIAAT IR (exemples showed by arrows); (b) BAD-LAMP labeling is found in the vicinity of synaptic density (arrowhead)

We generated Bad-Lamp conditionally mutant mice. In these animals all functional proteins can be deleted by loxP/CRE recombination. These animals were crossed to different inducer lines allowing gene inactivation in a controlled manner, ranging from entirely BadLamp deficient animals to lines in which only the strongly BadLamp positive striatum is mutated.

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