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Title: "BEACH domain proteins as a novel molecular principle in subcellular protein traffic and human diseases: LRBA is involved in olfaction and in the ciliary targeting of a heterotrimeric G-protein".

Abstract:

BEACH domain proteins constitute a family of eight members in humans, with emerging roles in membrane dynamics and membrane protein targeting. Genetic defects of LYST are responsible for perturbations of the biogenesis of lysosomes and secretory granules in the *beige* mouse and in Chediak-Higashi Syndrome patients (BEACH = “beige and Chediak-Higashi”), and mutations in NBEAL2 cause dysgenesis of thrombocyte secretory granules in Gray Platelet Syndrome patients.

Neurobeachin (Nbea) was discovered by my laboratory as a component of synaptic plasma membranes. Neurobeachin KO mice display a complete block of evoked transmission at the neuromuscular junction, causing perinatal death through breathing paralysis, and partial impairments of signaling by central synapses (excitatory and inhibitory) with pre- and postsynaptic components. Heterozygous Nbea KO mice develop overweight and display abnormal feeding behaviour, and NBEA gene polymorphisms are associated with increased body weight and Body Mass Index in human cohorts. Rearrangements of the NBEA gene have also been detected in small subgroups of patients with autism or with multiple myeloma (plasmacytoma). The Nbea isoform, LRBA, has been implicated in immune response and cancer cell proliferation. LRBA-mutant humans are affected by severe immune deficiency, whereas LRBA KO mice are viable but display sensory and renal abnormalities. At the molecular level, the Nbea KO impairs the postsynaptic targeting of several ionotropic neurotransmitter receptors, whereas the LRBA KO affects the targeting of G_{olf} to olfactory cilia. With these results, BEACH proteins continue to emerge as a novel and scarcely explored molecular principle in the orchestration of subcellular protein traffic and in human disease.