Using correlative light/electron microscopy (CLEM) approaches to study the regulation of metabolic enzyme self-assembly in cell starvation

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The functional organization of cells involves numerous intracellular structures composed of macromolecular assemblies of proteins and/or RNA. In cells, the formation of these self-assemblies of molecules is tightly regulated, with functional consequences. Some metabolic enzymes in particular are able to self-assemble into distinct punctate or filamentous domains, which suggest a role of molecular self-assembly in the regulation of metabolic activity. It was shown previously in a large-scale assay of GFP-tagged proteins that upon nutrient starvation in yeast, the Gln1 enzyme, which catalyzes the ATP-dependent synthesis of glutamine from glutamate and ammonium redistributed from a diffuse intracellular localization to fluorescent foci. In the present study we have used correlative light/electron microscopy (CLEM) of mCherry tagged Gln1, to investigate the Gln1 intracellular organization in response to cell starvation. Our results show that in cell starvation, Gln1 assembles into filamentous structures at the mesoscale. At the ultrastructural level in electron microscopy, these filaments are composed of bundles of Gln1-containing fibers. These fibers are consistent with a long range back-to self-assembly of Gln1 homodecamers. The Gln1 filaments are rapidly disassembled when nutriments are restored. Our hypothesis is that the formation of Gln1 filaments negatively regulates the function of this enzyme without degradation of the protein, which can rapidly be reactivated by filament disassembly, thus allowing a rapid and efficient control of cell metabolism.