

Active Interaction Mapping reveals the hierarchical organization of autophagy

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We have developed a general progressive procedure, Active Interaction Mapping, to guide assembly of the hierarchy of functions encoding any biological system. Using this process, we assemble an ontology of functions comprising autophagy, a central recycling process implicated in numerous diseases. A first-generation model, built from existing gene networks in *Saccharomyces*, captures most known autophagy components in broad relation to vesicle transport, cell cycle and stress response. Systematic analysis identifies synthetic-lethal interactions as most informative for further experiments; consequently, we saturate the model with 156,364 such measurements across autophagy-activating conditions. These targeted interactions provide more information about autophagy than all previous datasets, producing a second-generation ontology of 220 functions. Approximately half are new, in which we confirm roles for Gyp1 at the phagophore-assembly site, Atg24 in cargo engulfment, Atg26 in cytoplasm-to-vacuole targeting, and Ssd1, Did4 and others in selective and non-selective autophagy.