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Characterization of the autophagoproteasome a novel cell clearing organelle in eukaryotic cells

Paola Lenzi [1] - Federica Fulceri [1] - Stefano Gambardella [2] - Federica Cantini [1] - Larissa Ryskalin [1] - Gloria Lazzeri [1] - Francesco Fornai [2]

[1] Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy - [2] IRCCS, Neuromed, Pozzilli (IS), Italy

The autophagy (ATG) and Ubiquitin-Proteasome (UP) pathways clear proteins and membranes from eukaryotic cells. Their dysfunction is associated with systemic diseases, and neuronal degeneration. These pathways are commonly viewed as independent biochemical steps owing pathway-specific enzymatic activity taking place within different, site specific cell domains. While ATG is placed within a double/multiple membrane structure named autophagosome, the UP pathway is viewed as a protein complex dispersed in the cytosol. Scattered recent data provided functional evidence suggesting an interplay between ATG and UP. We recently provided morphological and biochemical evidence suggesting the existence of a close relationship between ATG and UP which may converge to form a novel organelle named autophagoproteasome. In the present study we characterized the autophagoproteasome by using various experimental approaches in vitro and in vivo. We studied the autophagoproteasomes in baseline conditions, following mTOR inhibition, and during specific neurotoxic treatments. The quantitative evaluation of ATG and UP component within autophagoproteasomes was carried out by confocal microscopy and ultrastructural morphometry. The number of autophagoproteasomes increases following mTOR inhibition. Again, specific neurotoxins as well as endogenous neurotransmitters modulate the expression of autophagoproteasomes. Remarkably, within autophagoproteasomes the relative amount of ATG compared with UP components varies depending on experimental conditions. Despite its morphological novelty the autophagoproteasome appears to be the organelle where ATG and UP (originally regarded to be independent structures) co-exist and share the catalytic activity. In addition, ATG and UP co-immunoprecipitate, suggesting a reciprocal binding and functional interplay.

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Keywords

Autophagy; proteasome; ubiquitination; protein clearing pathways.