Novel Insights into the Regulation of Autophagy in Saccharomyces Cerevisiae

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Autophagy is an evolutionarily conserved pathway for the degradation of intracellular contents. How autophagy is regulated, especially upon changes in metabolic and nutritional state, remains poorly understood. In Saccharomyces cerevisiae, autophagy is normally triggered by nutrient starvation. However, by using a prototrophic strain, I discovered that autophagy can be strongly induced upon switch from a rich medium (YPL) to a minimal medium (SL) without nutrient starvation. This new autophagy-inducing condition was termed SL-induced autophagy. Growth measurement confirmed that SL-induced autophagy was important for cellular homeostasis and growth following medium switch.

A genetic screen uncovered IML1, NPR2, NPR3 and PBP1, which are all required for SL-induced autophagy, but not for nitrogen-starvation-induced autophagy. Iml1p, Npr2p and Npr3p function in the same complex and regulate autophagosome formation. During SL-induced autophagy, Iml1p can localize to the pre-autophagosomal structures, consistent with the role of the Iml1p complex in autophagosome formation. Moreover, a conserved domain in Iml1p was identified to be required for SL-induced autophagy as well as complex formation.

I discovered that sulfur containing amino acids, but not non-sulfur containing amino acids, can specifically inhibit SL-induced autophagy. I further demonstrated that cysteine is a key metabolite that inhibits SL-induced autophagy by regulating cellular processes related to cysteine metabolism. Cysteine does not suppress SL-induced autophagy by regulating oxidative stress, protein urmylation and thiolation of cytosolic tRNAs. Future studies will be required to reveal the exact mechanism through which cysteine inhibits SL-induced autophagy.

I also discovered that autophagy can be significantly induced upon depletion of a Fe-S cluster containing protein, Rli1p, and other factors that are also involved in rRNA processing and translation initiation. Interestingly, IML1, NPR2, NPR3 and PBP1 are also important for Rli1p-depletion-induced mitophagy. These results strongly suggest the mechanistic link between SL-induced autophagy and ribosome biogenesis or translation regulation.

Collectively, my studies have demonstrated the existence of additional mechanisms that regulate autophagy in response to relatively more subtle changes in metabolic and nutritional state.