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# Spermidine and resveratrol induce autophagy by distinct pathways converging on the acetylproteome

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Autophagy protects organelles, cells, and organisms against several stress conditions. Induction of autophagy by resveratrol requires the nicotinamide adenine dinucleotide–dependent deacetylase sirtuin 1 (SIRT1). In this paper, we show that the acetylase inhibitor spermidine stimulates autophagy independent of SIRT1 in human and yeast cells as well as in nematodes. Although resveratrol and spermidine ignite autophagy through distinct mechanisms, these compounds stimulate convergent pathways that culminate in concordant modifications of the acetylproteome. Both agents favor convergent deacetylation and acetylation reactions in the cytosol and in the nucleus, respectively. Both resveratrol and spermidine were able to induce autophagy in cytoplasts (enucleated cells). Moreover, a cytoplasm-restricted mutant of SIRT1 could stimulate autophagy, suggesting that cytoplasmic deacetylation reactions dictate the autophagic cascade. At doses at which neither resveratrol nor spermidine stimulated autophagy alone, these agents synergistically induced autophagy. Altogether, these data underscore the importance of an autophagy regulatory network of antagonistic deacetylases and acetylases that can be pharmacologically manipulated.