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Longevity-relevant regulation of autophagy at the level of the acetylproteome

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The acetylase inhibitor, spermidine and the deacetylase activator, resveratrol, both induce autophagy and prolong life span of the model organism *Caenorhabditis elegans* in an autophagy-dependent fashion. Based on these premises, we investigated the differences and similarities in spermidine and resveratrol-induced autophagy. The deacetylase sirtuin 1 (SIRT1) and its orthologs are required for the autophagy induction by resveratrol but dispensable for autophagy stimulation by spermidine in human cells, *Saccharomyces cerevisiae* and *C. elegans*. SIRT1 is also dispensable for life-span extension by spermidine. Mass spectrometry analysis of the human acetylproteome revealed that resveratrol and/or spermidine induce changes in the acetylation of 560 peptides corresponding to 375 different proteins. Among these, 170 proteins are part of the recently elucidated human autophagy protein alterations in the acetylproteome regulate autophagy at multiple levels.

Key words: aging, cancer, *Caenorhabditis elegans*, HCT116, *Saccharomyces cerevisiae*, SILAC

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Macroautophagy (which we refer to as "autophagy") constitutes an essential mechanism of adaptation to external or internal stress that increases the fitness of individual cells and even entire organisms. Autophagy plays a cardinal role in cellular homeostasis, facilitates the mobilization of energy reserves when external resources are scarce, and is indispensable for the removal of toxic protein aggregates and damaged organelles. At the organismal level, autophagy can mediate cardioprotection and neuroprotection (for instance in the context of ischemic preconditioning), delay the pathogenic manifestations of aging and prolong life span.

A myriad of distinct stimuli and noxious agents can induce a rapid homeostatic autophagy that becomes apparent within minutes or hours. Accordingly, there is