Addendum

Inducing autophagy harmlessly

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An important role of autophagy in the clearance of misfolded proteins in neurons has been demonstrated. The challenge now is to see if we can develop small molecules that can induce autophagy without causing cellular damage.

Although the presence of ubiquitinated protein aggregates in the form of neuro-fibrillary tangles (NFT) or cytoplasmic inclusion bodies is common in neurodegenerative diseases, there is as yet no direct evidence that a failure in the proteasomal system is responsible for the accumulation of such abnormal proteins. On the other hand, the accumulation of polyubiquitinated protein aggregates in mice that are specifically deficient for atg5 or atg7 in neurons provides strong evidence for the role of autophagy in the removal of misfolded proteins. A defect in autophagy is particularly detrimental for the survival and function of neurons, which are postmitotic and long-lived and, therefore, have no option for turnover and/or dilution of misfolded proteins by cell division.

Most chronic neurodegenerative disorders start later in life. This is particularly striking with Huntington’s disease (HD); although 100% of patients who inherit a mutant htt allele will manifest the disorder sometime in their lives, they may live normally for 40–50 years without any symptoms, while carrying the full amount of the mutant huntingtin (Htt) protein in their neurons. Thus, it has been proposed that the neurons of younger individuals are able to detoxify the mutant Htt and, by the same notion, the neurons in older individuals are less capable of detoxifying the mutant protein. Since autophagy has been shown to be highly capable of removing misfolded proteins, a decline in autophagy function during aging has led to the identification of 8 true autophagy inducers and, most interestingly, 7 out of 8 autophagy inducers are FDA approved drugs for the treatment of neurological, and cardiac as well as gastrointestinal disorders.

Although it remains to be seen if any of these 7 FDA approved drugs are potent and specific enough for reducing the load of toxic misfolded proteins and ameliorating neuronal degeneration in animal models of HD and eventually in humans, the study by Zhang et al. provides a proof of principle for the possibility of discovering compounds that can induce autophagy with minimum cytotoxicity. Maybe one day we will be able to induce autophagy briefly in our neurons by taking a pill once in a while, and that will be enough to clear out misfolded proteins to prevent the onset of chronic neurodegenerative diseases.

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