Boosting protein quality control: A strategy against neurodegenerative diseases

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The deposition of misfolded proteins is a defining feature of many age-dependent human diseases, including the increasingly prevalent neurodegenerative diseases. Cells normally strive to ensure that proteins get correctly folded and have powerful and sophisticated protein quality control mechanisms to maintain protein homeostasis (proteostasis). However, with age, the cellular defense systems against misfolded proteins get overwhelmed, leading to the accumulation of misfolded proteins with devastating consequences for cells and organisms.

Improving the cells' ability to deal with misfolded proteins should represent a generic approach to reduce pathology in diverse protein misfolding diseases. My lab has identified powerful strategies to help cells survive when protein quality control fails and implemented some of these strategies in mice. Through unbiased approaches, we have identified small drug-like molecules that safely boost a natural defense system against misfolded.

The small molecules we have identified inhibit serine/threonine phosphatases controlling the termination of a proteostatic pathway, an interesting finding because phosphatases were previously thought to be undruggable. The selective inhibitors discovered in the lab have demonstrated therapeutic effects in various models of neurodegenerative diseases. This work demonstrates that generic approaches aimed at helping cells to survive protein quality control failures can be useful to prevent protein misfolding diseases, including the devastating neurodegenerative diseases. One of these inhibitors, Sephin1, has passed through favorable Phase 1 clinical trials in 2019 and is being developed for Charcot-Marie-Tooth disease. Last year, Guanabenz was found beneficial in a phase 2 clinical trial in ALS, 10 years after we reported its activity in helping cells to survive protein misfolding insults.