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NEURODEGENERATIVE DISEASE

Yeast cells reveal new target for Parkinson's disease

Cell-based assays can be powerful tools for investigating the mechanisms underlying human diseases and identifying lead compounds. In the case of neurodegenerative diseases, however, it is difficult to establish robust neuronal phenotypes that are amenable to high-throughput screening. Two studies from Susan Lindquist's laboratory, published in *Science*, highlight how yeast that have been engineered to express proteins that are associated with neurodegenerative diseases, such as α-synuclein, can be used to overcome this problem and facilitate the discovery of new drug targets and potential treatments.

Expression of α-synuclein in yeast disrupts vesicle trafficking, ion homeostasis and mitochondrial function (as in neurons). It also strongly inhibits yeast growth, so the authors were easily able to screen for compounds that are able to restore growth and thus protect from α-synuclein-mediated toxicity. In the first study, Tardiff *et al.* show that one such compound, an *N*-aryl benzimidazole (NAB), also protects neurons in three Parkinson's disease models: *Caenorhabditis elegans* dopaminergic neurons expressing human α-synuclein, embryonic rat midbrain neurons expressing an α-synuclein mutation (A53T) that causes selective loss of dopaminergic neurons, and cortical neurons derived from pluripotent stem cells from a patient with Parkinson's disease. These findings suggest that NAB's target and mechanism of action is conserved from yeast to humans.

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High concentrations of NAB inhibit the growth of wild-type cells, so by identifying genetic alterations that restore it, the authors hoped to uncover NAB's target. Using NAB2 (the most potent of the 29 NAB analogues that they synthesized), they screened three large libraries of mutated yeast cells in search of genetic alterations that allowed growth at high concentrations. They found that the E3 ligase Nedd4 (neural precursor cell expressed developmentally downregulated protein 4; also known as Rsp5), which promotes endosomal transport, is the main mediator of the effects of NAB. Further experiments show that whereas NAB promotes Rsp5-dependent processes, α-synuclein disrupts them, which indicates that targeting this form of endosomal transport is key to restoring vesicle trafficking and rescuing cells from α-synuclein-mediated toxicity.

In a second study, Chung *et al.* focus on characterizing the cortical neurons derived from induced pluripotent stem cells from patients carrying α-synuclein mutations associated with a high risk of developing Parkinson's disease dementia, with the aim of identifying early pathogenic phenotypes as the neurons aged *in vitro*. They found similar features to those in yeast cells expressing α-synuclein and in the brains of post-mortem patients: nitrosative stress, accumulation of endoplasmic reticulum-associated degradation (ERAD) substrates and ER stress. Strikingly, exposure to NAB2 reversed the damage in these neurons through the same target, as lentiviral expression of Nedd4 phenocopied the effect.

Together, these studies highlight the use of yeast cells and reprogrammed patients' cells as useful platforms for central nervous system (CNS) drug discovery. Future work on optimizing NAB and preclinical testing in animal models will be eagerly awaited.

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ORIGINAL RESEARCH PAPERS Tardiff, D. F. *et al.* Yeast reveal a "druggable" Rsp5/Nedd4 network that ameliorates α-synuclein toxicity in neurons. *Science* **342**, 979–983 (2013) | Chung, C. Y. *et al.* Identification and rescue of α-synuclein toxicity in Parkinson patient-derived neurons. *Science* **342**, 983–987 (2013)