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Researchers find potential in yeast for selecting Lou Gehrig's disease drugs

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Researchers from the University of Pennsylvania School of Medicine are developing a novel approach to screen for drugs to combat neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, using yeast cells. In recent months a number of mutations have been found in a disease protein called TDP-43, which is implicated in ALS and certain types of frontotemporal dementia (FTD).

“We've created a yeast model, the same cells that bakers and brewers use to make bread and beer, to express TDP-43,” explains lead author Aaron D. Gitler, PhD, Assistant Professor of Cell and Developmental Biology. “Remarkably, this protein formed clumps in our simple yeast cells just like it does in human nerve cells. In our paper we determine which segments of the mutated TDP-43 protein cause it to aggregate and which parts cause it to be toxic.” Gitler and colleagues report their findings in this week’s advance online issue of the *Proceedings of the National Academy of Sciences*.

Two years ago, other Penn investigators found that TDP-43 accumulated abnormally in post-mortem brain or nervous system tissue from individuals diagnosed with either ALS or FTD. TDP-43 is normally involved in RNA and DNA processing, among other cellular tasks. The recent TDP-43 mutation studies confirm the protein’s role in causing disease.

The clumping process of proteins takes decades in humans but the researchers could model the process within a matter of hours in yeast

cells. This now allows for rapid genetic screening to identify proteins that can reverse the harmful effects of the disease protein; visualizing the clumping; and testing molecules that could eliminate or prevent clumping.

“Our yeast model will be a powerful tool for performing large-scale drug screens to look for small molecules that can prevent TDP-43 from aggregating or that can protect cells from aggregated TDP-43,” notes Gitler.

Normally, TDP-43 stays in the nucleus, but in ALS and FTD it somehow gets sequestered into the cell’s cytoplasm, where it forms clumps. “When we put TDP-43 in yeast cells at normal human levels, it remained in the nucleus,” explains Gitler. “However, when it was expressed at higher levels, thereby overwhelming the quality control systems of the cell, TDP-43 clumped in the cytoplasm. At even higher levels, TDP-43 became toxic to the yeast cells, making them unable to grow.” This experiment suggests, for the first time, that TDP-43 clumps can be a direct cause of cell toxicity.

In earlier studies at Penn, researchers found fragments of TDP-43 that were abundant in the clumps found in the post-mortem tissue of ALS and FTD patients. Knowing this, Gitler and colleagues chopped TDP-43 into many fragments to find the segments that are responsible for clumping and toxicity. They found a very similar segment that was also toxic to yeast cells. Designs of future drugs will depend on what part of the TDP-43 protein needs to be disabled.

The researchers are able to overexpress every yeast gene to determine which genes can rescue the yeast cells from the TDP-43 toxicity. In addition to these genetic screens, Gitler and colleagues are pursuing drug screens with their TDP-43 model. “We can screen hundreds of thousands of small molecules to see which can get into a yeast cell and

prevent TDP-43 from being toxic," says Gitler. "Then we can take the hits we find and test them in animal models. We have already made mutations identical to what have been found in patients and have introduced those in the yeast model."

Source: University of Pennsylvania