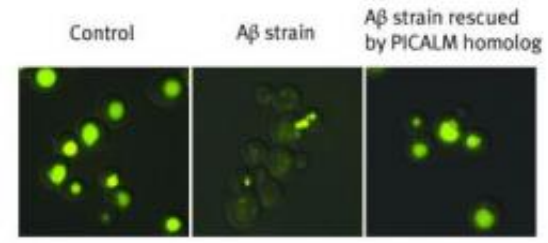
Yeast model connects Alzheimer's disease risk and amyloid beta toxicity

October 27 2011



Using yeast cells, a team of Whitehead scientists in the lab of Whitehead Member Susan Lindquist investigated the harmful effects of amyloid beta (Aβ), a peptide whose accumulation in amyloid plaques is a hallmark of AD. Work by the lab indicates that Aβ disrupts normal cellular trafficking, with clathrin-mediated endocytosis being specifically vulnerable. Under normal conditions, the membrane bound receptor Ste3 (green) is subject to clathrin-mediated endocytosis and is trafficked to the cell's vacuole (left). In Aβ expressing yeast cells, Ste3 is not localized to the vacuole, but is dispersed in foci throughout the cell, indicating that endocytic trafficking is perturbed (center). Expression of the yeast homolog of PICALM, one of the most highly validated human AD risk factors, restores normal trafficking in Aβ-expressing yeast, and Ste3 is again localized in the vacuole (right). Credit: Courtesy of Science/AAAS

In a development that sheds new light on the pathology of Alzheimer's disease (AD), a team of Whitehead Institute scientists has identified connections between genetic risk factors for the disease and the effects of a peptide toxic to nerve cells in the brains of AD patients.

The scientists, working in and in collaboration with the lab of Whitehead Member Susan Lindquist, established these previously unknown links in an unexpected way. They used a very simple cell type—yeast cells—to investigate the harmful effects of amyloid beta (Aβ), a peptide whose accumulation in amyloid plaques is a hallmark of AD. This new yeast model of Aβ toxicity, which they further validated in the worm *C. elegans* and in rat neurons, enables researchers to identify and test potential genetic modifiers of this toxicity.

"As we tackle other diseases and extend our lifetimes, Alzheimer's and related diseases will be the most devastating personal challenge for our families and one the most crushing burdens on our economy," says Lindquist, who is also a professor of biology at Massachusetts Institute of Technology and an investigator of the Howard Hughes Medical Institute. "We have to try new approaches and find out-of the-box solutions."

In a multi-step process, the researchers were able to introduce the form of Aβ most closely associated with AD into yeast in a manner that mimics its presence in human cells. The resulting toxicity in yeast reflects aspects of the mechanism by which this protein damages neurons. This became clear when a screen of the yeast genome for genes that affect Aβ toxicity identified a dozen genes that have clear human homologs, including several that have previously been linked to AD risk by genome-wide association studies (GWAS) but with no known mechanistic connection.

With these genetic candidates in hand, the team set out to answer two key questions: Would the genes identified in yeast actually affect Aβ toxicity in neurons? And if so, how?

To address the first issue, in a collaboration with Guy Caldwell's lab at the University of Alabama, researchers created lines of *C. elegans* worms

expressing the toxic form of Aβ specifically in a subset of neurons particularly vulnerable in AD. This resulted in an age-dependent loss of these neurons. Introducing the genes identified in the yeast that suppressed Aβ toxicity into the worms counteracted this toxicity. One of these modifiers is the homolog of PICALM, one of the most highly validated human AD risk factors. To address whether PICALM could also suppress Aβ toxicity in mammalian neurons, the group exposed cultured rat neurons to toxic Aβ species. Expressing PICALM in these neurons increased their survival.

The question of how these AD risk genes were actually impacting Aβ toxicity in neurons remained. The researchers had noted that many of the genes were associated with a key cellular protein-trafficking process known as endocytosis. This is the pathway that nerve cells use to move around the vital signaling molecules with which they connect circuits in the brain. They theorized that perhaps Aβ was doing its damage by disrupting this process. Returning to yeast, they discovered that, in fact, the trafficking of signaling molecules in yeast was adversely affected by Aβ. Here again, introducing genes identified as suppressors of Aβ toxicity helped restore proper functioning.

Much remains to be learned, but the work provides a new and promising avenue to explore the mechanisms of genes identified in studies of disease susceptibility.

"We now have the sequencing power to detect all these important disease risk alleles, but that doesn't tell us what they're actually doing, how they lead to disease," says Sebastian Treusch, a former graduate student in the Lindquist lab and now a postdoctoral research associate at Princeton University.

Jessica Goodman, a postdoctoral fellow in the Lindquist lab, says the yeast model provides a link between genetic data and efforts to

understand AD from the biochemical and neurological perspectives.

"Our yeast model bridges the gap between these two fields," Goodman adds. "It enables us to figure out the mechanisms of these risk factors which were previously unknown."

Members of the Lindquist lab intend to fully exploit the yeast model, using it to identify novel AD risk genes, perhaps in a first step to determining if identified genes have mutations in AD patient samples. The work will undoubtedly take the lab into uncharted territory.

More information: "Functional Links Between Aβ Toxicity, Endocytic Trafficking and Alzheimer's Disease Risk Factors in Yeast" *Science*, October 28, 2011.

Provided by Whitehead Institute for Biomedical Research