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Modeling Parkinson's Disease in the Budding Yeast, Saccharomyces cerevisiae

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ABSTRACT

Parkinson's Disease (PD) is the second most common, incurable neurodegenerative disorder worldwide. PD patients have accumulations of abnormal proteins called Lewy Bodies (LBs) within their neurons that trigger cell death. Damaged and dead neurons lead to decline in dopamine levels, triggering the symptoms of Parkinson's such as muscle stiffness, tremors, and slowed movement. Numerous studies have shown that the human protein, α-synuclein and tau, are two major components of Lewy Bodies. To study the relationship between protein aggregation and cell death, we have created a system to co-overexpress human alpha-synuclein fused to GFP and human tau fused to mCherry in the budding yeast, *Saccharomyces cerevisiae*. Preliminary data suggests that low levels of α-synuclein-GFP appear to localize to the yeast cell membrane while tau-mCherry localizes to the vacuole.

INTRODUCTION

Alpha-synuclein and tau are proteins located in the neurons of mammalian cells. The α-synuclein protein is believed to play a key role in monitoring the concentration neurotransmitters as well as membrane binding. The tau protein is thought to stabilize microtubules and are found in abundance in neurons. Two strains of *Saccharmocyes cerevisiae* (hitox and lotox) that overexpress α-synuclein were transformed with tau. to create a system that colocalizes both proteins to model the formation of Lewy Bodies.

FIGURE 1: Accumulations of Lewy Bodies Composed of Tau and α-Synuclein Leads Is Linked to Parkinson's Disease Progression

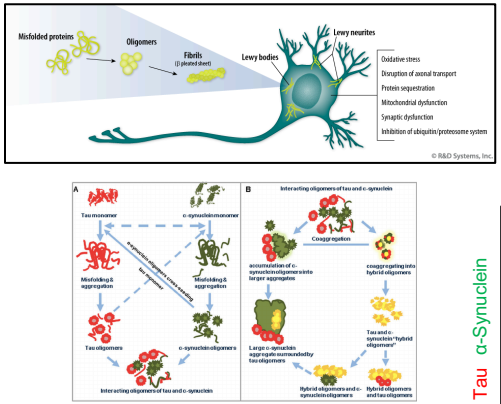


FIGURE 1: Aggregation of α-synuclein and tau have been linked to the formation of Lewy Bodies. The abnormal accumulation of both proteins triggers cell death, leading to symptoms of Parkinson's Disease.

FIGURE 2: Human Tau and Human α-Synuclein can be Expressed in Yeast

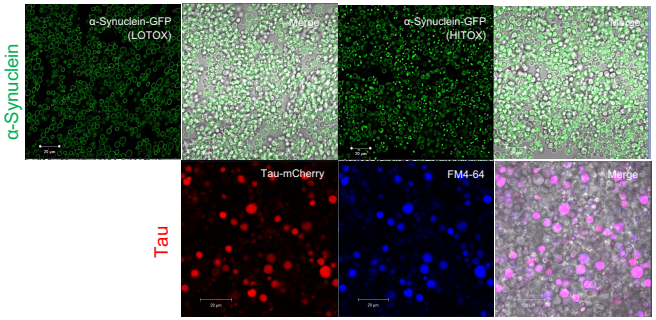
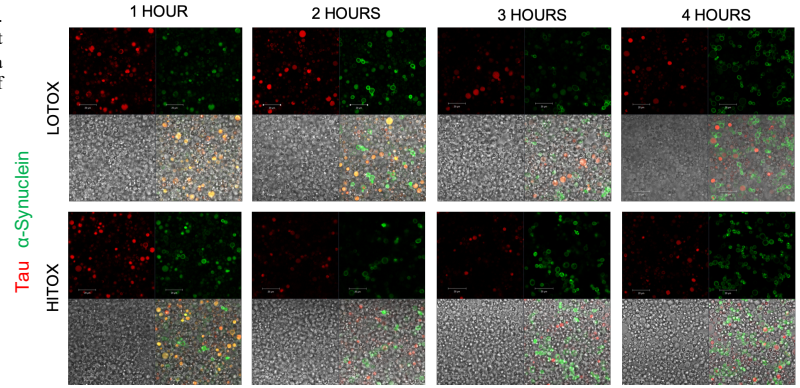


FIGURE 2: The wildtype LOTOX strain was grown in YEPGlu media for 24 hours. Cells were then transferred to YEPRaf media and then transferred to YEPGal after 4 hours to induce α-synuclein expression. The wildtype W303 strain was transformed with a plasmid expressing human Tau and grown in SD-trp liquid media for 24 hours. Cells were transferred to SRaf-Trp media and stained with FM464. Cells were transferred to SGal-Trp to induce the tau protein. Both strains were imaged using a Zeiss LSM 700 laser confocal microscope.

FIGURE 3: Colocalization of Tau and α-Synuclein Decreases Over Time



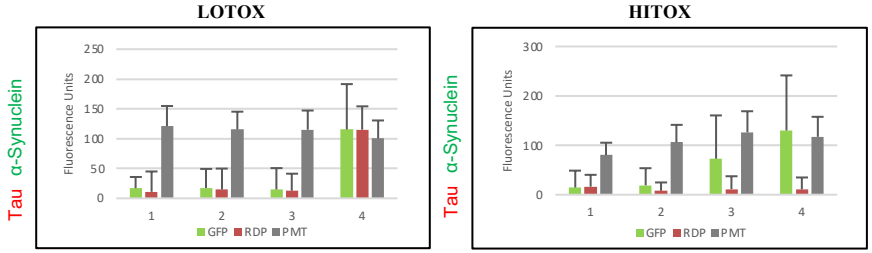


FIGURE 3: LOTOX and HITOX were transformed with a plasmid expressing Tau. Both strains were grown in SD-trp for 24 hours and transferred to Sraff-trp media. After 3 hours, the cells were transferred to SGal-trp to induce both proteins. The cells were imaged for 4 hours. The colocalization of proteins decreases as time progresses. The fluorescence of GFP, RDP, and PMT was quantified. The fluorescence of GFP increases as time progresses.

FIGURE 4: Tau and α-Synuclein Have Distinct Cellular Localizations After 24 Hours

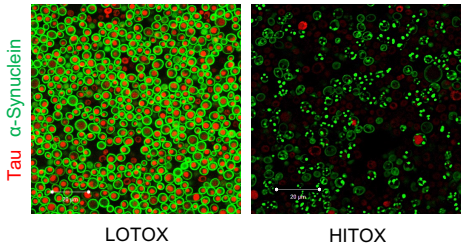


FIGURE 4: The LOTOX and HITOX strains imaged after 24 hours of induction showed no overlap.

FIGURE 5: Altering the Relative Expression of Tau and α-Synuclein Changes Tau Protein Expression

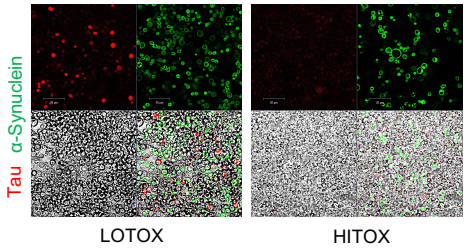


FIGURE 5: Both strains were transformed with a plasmid expressing Tau with a copper promoter. The cells were grown in SD-trp liquid media for 24 hours, Cells were transferred to Sraff-trp and then SGal-trp to induce α-synuclein. After 4 hours, a 100 mM copper sulfate was added to the culture to induce tau. Both strains were imaged after 5 hours of tau induction.

CONCLUSIONS

- Lewy Bodies can successfully be modeled in yeast
- Colocalization of tau and α-Synuclein decreases over time

FUTURE PLANS

- Continue to alter the relative expression of Tau and α-Synuclein
- Perform drug therapies on the cells to hopefully alleviate aggregation

ACKNOWLEDGEMENTS

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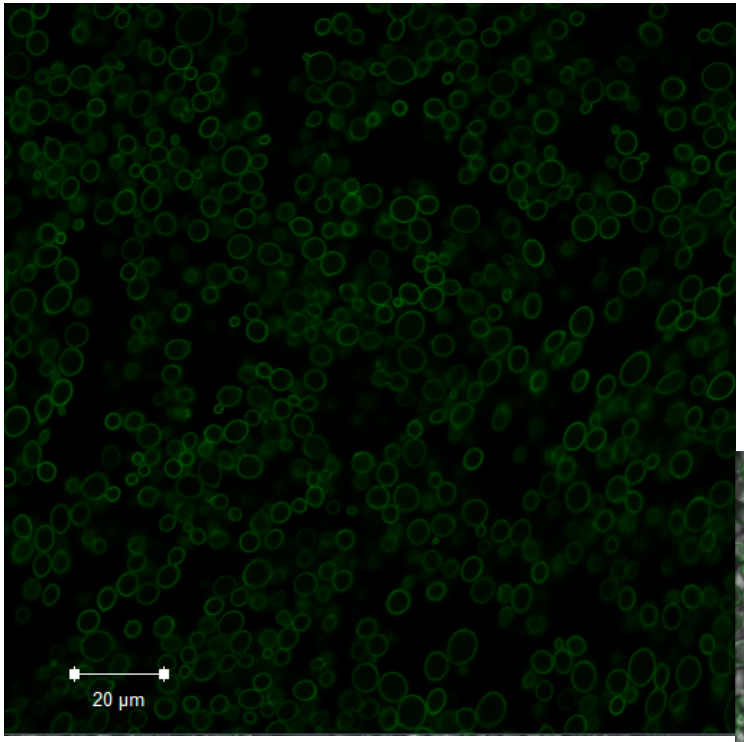
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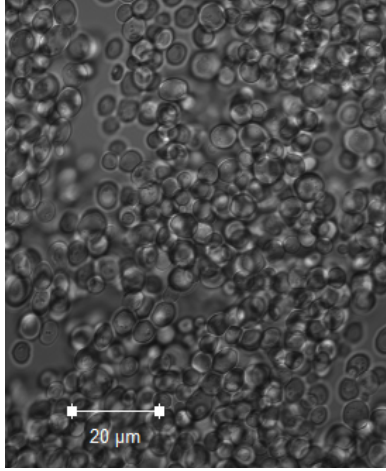
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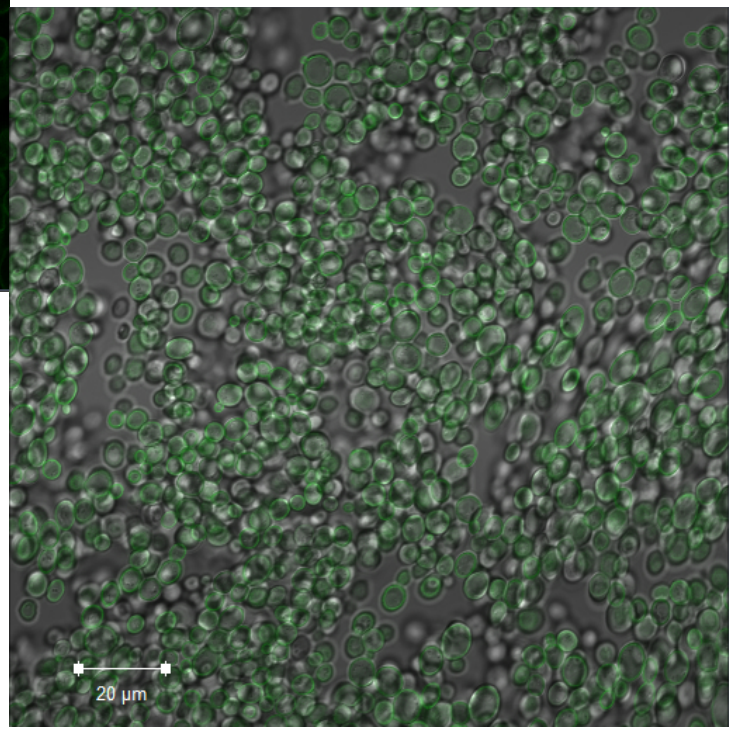
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