Baker's yeast shows potential for combating neurological conditions

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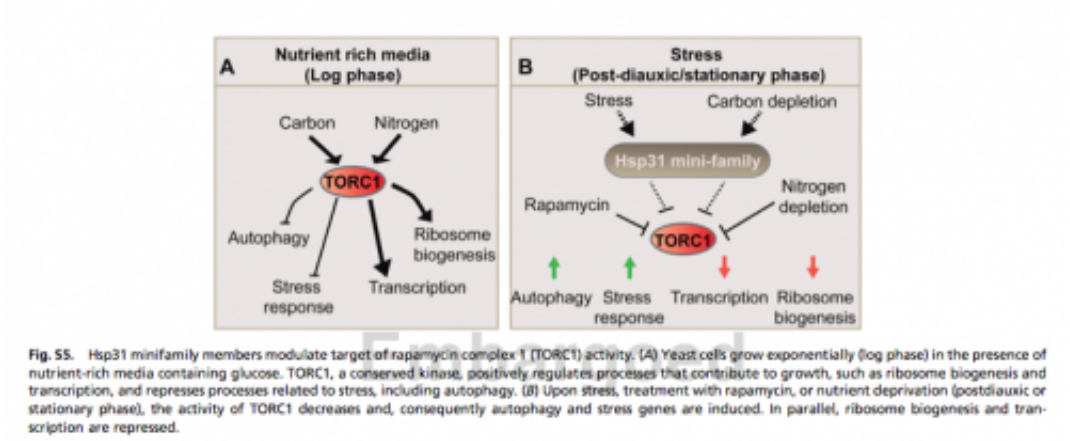

Fig. S5. Hsp31 minifamily members modulate target of rapamycin complex 1 (TORC1) activity. (A) Yeast cells grow exponentially (log phase) in the presence of nutrient-rich media containing glucose. TORC1, a conserved kinase, positively regulates processes that contribute to growth, such as ribosome biogenesis and transcription, and represses processes related to stress, including autophagy. (B) Upon stress, treatment with rapamycin, or nutrient deprivation (postdiauxic or stationary phase), the activity of TORC1 decreases and, consequently autophagy and stress genes are induced. In parallel, ribosome biogenesis and transcription are repressed.

The Hsp31-family genes modulate the activity of the TOR complex, a central regulator of several important functions in the cell. This new knowledge opens novel perspectives for therapeutic intervention in cancer and Parkinson's disease by modulating the activity of the Hsp31-family of genes. Credit: (c) *PNAS*

A humble ingredient of bread – baker's yeast – has provided scientists with remarkable new insights into understanding basic processes likely involved in diseases such as Parkinson's and cancer.

In a new study published today in the journal *PNAS* (*Proceedings of the National Academy of Science*), the team from Germany, Leicester, and Portugal detail a new advance – describing for the first time a key feature in cellular development linked to the onset of these devastating

diseases.

The research team is from the University Medical Center Goettingen, University of Leicester, and Instituto de Medicina Molecular, Lisbon, directed by long-time collaborators and senior authors Professor Tiago Outeiro and Dr Flaviano Giorgini.

Professor Outeiro, of the University Medical Center Goettingen, Goettingen and Instituto de Medicina Molecular, Lisbon, said: "This work shows how taking advantage of simple model organisms might help us speed up the discovery of more complex biological processes. Yeast cells are really excellent living test tubes, with a powerful toolbox that enabled us to learn about the underpinnings of complex human disorders."

Dr Giorgini, of the world-renowned Department of Genetics, at the University of Leicester, added: "We are tremendously excited by our results. The family of proteins under investigation have always been a bit of a "black box", and a true understanding of what these proteins do at a cellular level - and why they are important - has remained elusive. This work provides a step into this darkness."

The current research takes advantage of the simplicity and genetic power of the baker's yeast Saccharomyces cerevisiae to understand basic cellular processes underlying Parkinson's disease. The team studied a family of proteins in yeast (Hsp31, Hsp32, Hsp33, and Hsp34) which are related to a human protein known as DJ-1. Mutations in the human DJ-1 protein cause early-onset inherited forms of Parkinson's disease, and alterations in the human protein have been associated with more common forms of Parkinson's disease as well. In addition, changes in DJ-1 function are also associated with certain forms of cancer.

Claire Bale, Research Communications Manager at Parkinson's UK,

commented: "This important research sheds new light on the root causes of Parkinson's.

"Although mutations in the DJ-1 gene cause rare inherited forms of the condition, we believe that understanding the role of this crucial protein and how it helps keep nerve cells healthy could be important for developing treatments that can help all people with Parkinson's. We look forward to hearing the results of future investigations in this emerging new area."

Professor Outeiro continued: "We reasoned that, by studying the yeast cousins of the human protein we would gain important insight into the function these proteins play, and understand why they may cause disease."

Dr Giorgini added: "Though the human protein DJ-1 has been linked to Parkinson's disease, its central cellular role is not well understood, and thus it is not clear why mutations in this protein cause this devastating disease. Our study sheds new light on what DJ-1 and related proteins are doing at a cellular level, and may thus ultimately have importance for better understanding Parkinson's."

The scientists discovered that the yeast versions of the human protein are important for maintenance of normal lifespan of the yeast cell and are involved in regulation of autophagy – a process which the cell employs to breakdown and recycle damaged cellular components. Lifespan and autophagy are central processes in the context of both Parkinson's disease and cancer. This work is critical because it provides a precise cellular role for DJ-1 family proteins, which links to some of the molecular functions previously ascribed to these proteins. This work could ultimately provide new insight into the mechanisms that contribute to Parkinson's and cancer.

Leonor Miller-Fleming, of the Instituto de Medicina Molecular, Lisbon and University of Leicester, said: "Our work is important because it suggests that human DJ-1 may function in a similar manner to the yeast version of this protein. We feel that similar studies should be performed with human DJ-1 in nerve cells, to clarify its function and to see if this contributes to the formation of Parkinson's disease. Ultimately, the detailed understanding of how these proteins function may enable us to come up with novel strategies to treat Parkinson's disease, cancer, and other related disorders."

The collaborators believe the next steps in the research are to better understand the details of how the DJ-1 family of proteins regulates autophagy, and if this applies in human neurons, particularly dopaminergic neurons, which are the nerve cells most sensitive to loss in the Parkinson's brain. Once the researchers build up on the findings they have now described, they will be in a better position to design novel strategies for therapeutic intervention.

Professor Outeiro explained: "This study highlights the importance of international collaborations and networks, in which different strengths are combined to yield novel insights into science. Importantly, this scientific collaboration is also based upon personal friendship between the two senior authors, which makes science ever more exciting and fun."

Dr Giorgini added: "In addition, this work was primarily spearheaded by a single PhD student – Leonor Miller-Fleming – who drove the project forward with passion and creativity, showing the importance of promoting, supporting and funding doctoral research."

Professor Outeiro said: "We were pioneers in the development of the first model of Parkinson's disease in yeast cells. With this work, we explored the powerful toolbox of yeast cells to learn about DJ-1 proteins,

also intimately linked to Parkinson's disease. We are basically adding pieces to this complicated puzzle, and getting one step closer to understanding the origin of this disorder."

More information: Yeast DJ-1 superfamily members are required for diauxic-shift reprogramming and cell survival in stationary phase, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1319221111

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