OXFORD
FEMS JOURNALS investing in science

FEMS Yeast Research, 18, 2018, foy083

doi: 10.1093/femsyr/foy083
Editorial

Editorial: Yeast cell aging and death

A conspicuous amount of knowledge about the molecular biology of the cell has come from studies on yeast *Saccharomyces cerevisiae*, mostly because of its unrivaled qualities as a toolkit for molecular genetics study. The discovery in the late 90's that this unicellular eukaryote also may activate cell death programs both physiologically, like mammalian apoptotic cell death (Madeo, Frohlich and Frohlich 1997), and under environmental stress, completed the yeast-toolkit. The first thematic issue on this topic of *FEMS Yeast Research* four years ago witnessed the noticeable amount of research carried out to get a deeper insight into the mechanisms of fundamental biological processes, already discovered in yeast, such as genetic stability and expression, cell cycle, organelle biogenesis and cross-talk. Indeed, it has been possible to study these processes with the added dimension to discover their function and interrelationships in cell homeostasis maintenance considering also the effect of environmental cues.

Although debated by the scientific community, the field of yeast regulated cell death research has been expanding to more and more bio-medical research themes, including aging, human diseases, cell stress response and metabolism. Research on ageing is one of the top medical priorities in developed societies and yeast represents an attractive model system for studying more complex phenomena that occur in higher eukaryotic cells, including cell division, ageing and apoptosis. While such research in a clinical setting is confronted with—and limited by—ethical issues, and since studying ageing, longevity and regulated cell death in metazoan models is time consuming and costly, yeast cells offer an attractive eukaryotic model.

Although it is now clear that yeast can indeed undergo cellular suicide, the corresponding terminology to describe this multifaceted process remains heterogeneous and potentially misleading. Thus, following the directions of the Nomenclature Committee on Cell Death (NCCD) and adapting them to the particularities of *S. cerevisiae*, the yeast cell death research community has recently proposed unified criteria for the definition of accidental, regulated and programmed forms of cell death in yeast based on a series of morphological and biochemical criteria (Carmona-Gutierrez *et al.* 2018). This has clearly defined for the first time the concept of 'yeast cell death', with significant progress being made at the phenotypical and mechanistic levels, including the finding that, similarly to higher eukaryotes, yeast can also engage in distinct cell death modalities.

The second scientific revolution of *S. cerevisiae* as a model organism for fundamental academic research as well as a biofactory for a wide range of industrial applications is already under way. On one hand, postgenomic systems biology research has been focusing on the global mapping of genetic interaction networks. The systematic analysis of trigenic interactions in yeast, invented and developed in the laboratory of Charles Boone at the University of Toronto, is definitely laying the basis for the first successful opportunity to modelling a cell (Kuzmin *et al.* 2018). On the other hand, the international Synthetic Yeast Genome Project, known as Yeast 2.0 or Sc2.0, is to create a fully man-made genome for *S. cerevisiae* in order to better understand the biological intricacies of eukaryotic semi-synthetic organisms. This will allow to more accurately predict and control the practical outcomes of genome engineering—as opposed to individual gene-based genetic engineering (Pretorius 2017).

Despite these promising developments, elucidation of the mechanisms and identification of molecules controlling the intricate network, which regulates cell homeostasis is still an urgent necessity, in order to fully grasp the benefits of a holistic approach to biomedical and biotechnological research. Thus, this thematic issue is a showcase for cutting-edge achievements in the knowledge on the molecular basis of many fundamental cellular processes governing cell homeostasis, thus highlighting the new age of yeast research in biomedicine and biotechnology. In particular, special attention is paid to molecular mechanisms of ageing and regulated cell death, pointing to yeast as a valuable model for studying the onset of diseases and for screening/design drugs able to interfere with these pathologies.

In this second thematic issue on yeast aging and cell death of *FEMS Yeast Research* we have collected and edited six Mini Reviews that provide an overview of cutting-edge research on fundamental processes, including RNA stability, nutrient sensing, proteostasis, lipotoxicity, mitochondrial–cytosol–nucleus communications and aging. Three mini-reviews deal with yeast multicellular communities, the potential of yeast mitochondria to develop mitochondrial systems biology and the use of yeast as a platform for anti-aging drug discovery.

Obesity and overweight are the adverse effects of excessive nutrition and they can be associated with metabolic alterations leading to metabolic syndrome. Although the exact etiology of metabolic syndrome is not known, unbalanced lipid metabolism in non-adipose tissues is considered to contribute to lipotoxicity, The use of yeast has provided important insights into the toxicity associated with exposure to excess fatty acids (FAs), diacylglycerol (DGs), sterols and ceramides. The minireview by Rockenfeller and Gourlay (doi: 10.1093/femsyr/foy034) recapitulates recent research advances on the Rim101 pathway and membrane contact sites in the context of lipotoxicity in yeast and offers an outlook for future research directions.

Received: 18 July 2018; **Accepted:** 8 August 2018

The RNA world comprises a broad class of molecules with different cellular functions, which are mainly classified as coding and non-coding RNAs. Both play different structural or functional roles within the cell and, for this reason, the study of RNA metabolism, including regulation, modification and stability of transcripts, represents a crucial milestone for understanding the biology of cells. Falcone and Mazzoni, in their minireview (doi: 10.1093/femsyr/foy050), summarize recent research on RNA stability and its connection with cell death and aging.

Target of Rapamycin (TOR) complex, the master regulator of cell growth and amino acid sensing, and its downstream effector Sch9 have been implicated in various age-related disorders. The Mini Review by Deprez *et al*. (doi:10.1093/femsyr/foy048) outline the current knowledge on the molecular mechanisms through which the TORC1–Sch9 signaling axis regulates lifespan in *S. cerevisiae*, unraveling the connections of TORC1 and Sch9 with yeast ageing by showing how downregulating TORC1–Sch9 signaling promotes lifespan extension by inducing a variety of physiological changes, thus providing additional clues on how their mammalian orthologues contribute to the mechanisms underpinning human ageing and health. In this context the Mini Review by Teng *et al*. (FEMSYR-18-02-0041) described the Whi2 as a newly identified negative regulator of cell growth in low amino acids although to date the biochemical functions of Whi2 remain unknown. The KCTD (potassium channel tetramerization domain) family proteins are shown as the mammalian homologues of Whi2 and cross-talk among nutrient sensing pathways is described.

The diversity of mechanisms controlling proteostasis in yeast is reviewed by Sampaio-Marques and Ludovico (doi:10.1093/femsyr/foy043), with particular emphasis on the developments that highlight the multidimensional nature of the proteostasis network as well as the age-dependent changes of this network.

Although microbial cells are considered unicellular organisms, they can form organized multicellular communities. The study of yeast cells in colonies provides some clues on multicellular development. In the minireview by Vachova and Palkova (doi: 10.1093/femsyr/foy033) are presented metabolic differences between particular yeast communities as well as the presence and functions of various differentiated cells, providing examples of the ability of these cells to develop different ways to cope with stress during community development and ageing.

Mitochondria are key cell organelles with a prominent role in both energetic metabolism and the maintenance of cellular homeostasis. The Mini Review by Guaragnella *et al*. (FEMSYR-18-03-0071) focuses on the key pathways that mediate nucleus–cytosol–mitochondria communications through both transcriptional regulation and proteostatic signaling. It highlights yeast that likely continues to serve as a productive model organism for mitochondrial research in the years to come. This is further featured in the overview of mitochondrial biology as known through yeast research, authored by Malina *et al*. (doi: 10.1093/femsyr/foy040). The authors provide an attractive outlook on how systems biology studies, including mathematical modeling, have allowed gaining new insight into mitochondrial function, and argue that this approach may enable us to gain a holistic view on how mitochondrial function interacts with different cellular processes.

Finally, yeast can be used as a platform for anti-aging drug discovery. For example, yeast-based studies led to the discovery of resveratrol or spermidine as potential anti-aging agents. Zimmermann *et al*. (FEMSYR-17-12-0215.R1) in their minireview present strategies for pharmacological anti-aging screens in yeast, discuss common difficulties and present recent studies that have used yeast for discovering both new drugs and their target.

Conflict of interest. none declare.

REFERENCES

Carmona-Gutierrez D, Bauer MA, Zimmermann A *et al*. Guidelines and recommendations on yeast cell death nomenclature. *EMBO Rep* 2018;**5**:1875–84.

Kuzmin E, VanderSluis B, Wang W *et al*. Systematic analysis of complex genetic interactions. *Science* 2018;**360**:eaao1729.

Madeo F, Frohlich E, Frohlich KU. A yeast mutant showing diagnostic markers of early and late apoptosis. *J Cell Biol* 1997;**139**:729–34.

Pretorius IS. Solving yeast jigsaw puzzles over a glass of wine: Synthetic genome engineering pioneers new possibilities for wine yeast research. *EMBO Rep* 2017;**18**:1875–84.

Sergio Giannattasio
Institute of Biomembranes, Bioenergetics and Molecular Biotechnologies,National Research Council, Via Amendola 165/a, I-70126 Bari, Italy
E-mail: s.giannattasio@ibiom.cnr.it

Cristina Mazzoni
Department of Biology and Biotechnologies “C. Darwin”, University of Rome “Sapienza”, Piazzale A. Moro 5, I-00185 Rome, Italy