Editorial

Yeast on the corner of life and death decisions

Cells are continuously facing exogenous and endogenous stressful conditions that threaten cellular homeostasis and elicit numerous molecular responses, resulting either in cell adaptation and survival or in cell demise. Several interconnected genetically conserved molecular pathways control the adaptive responses, as well as the decision to commit suicide. Understanding this intricate network is often hampered by the complexity of higher eukaryotic systems. Since the initial sequencing and functional analysis of the *Saccharomyces cerevisiae* genome, yeast has become a superb model and toolbox to unravel conserved and non-conserved components of pathways underpinning cell survival and death decisions in eukaryotic cells, as well as dissect their functional interactions. Hence, yeast cells may offer answers for understanding how a cell recognizes and repairs damage, maintains homeostasis, or conversely fails to cope with stress and dies. This evidence is crucial to understand the biological basis of aging, life span determination, several age-related disorders and other human pathologies.

This special issue of *Mechanisms of Ageing and Development* contains 11 peer-reviewed manuscripts, 6 revisions and 5 original studies, covering and highlighting the enormous potential of yeast cells to elucidate core cell death molecular mechanisms relevant to further understanding of aging and human disorders, as well as to identify novel therapeutic targets and carry drug-based screens.

The first manuscript of this special issue illustrates how heterologous expression of Bcl-2 family members in yeast cells provided important clues about their function and interactions. Bcl-2 family members are major regulators of mitochondrial membrane permeabilization and crucial determinants of cell death fate, though it is complex to decipher the intricate networks regulating pro- and anti-apoptotic members. Manon and co-workers offered a very comprehensive overview on how yeast, where obvious Bcl-2 homologues are absent, help elucidating the steps leading to Bax activation. These studies impact on the design of novel strategies to reactivate Bax in apoptosis-deficient cells such as tumoral cells.

In contrast, the conservation of core survival and death pathways among eukaryotic cells makes yeast a powerful tool to understand the mechanistic aspects of life and death processes of higher eukaryotes. The review by Azopardi et al. addresses the usefulness of yeast as a model to elucidate the interplay between molecular regulators shared by survival and death pathway such as cell cycle, autophagy and apoptosis. Recent evidence also suggested that a regulated and conserved communication between different cellular organelles, particularly endoplasmic reticulum

and mitochondria, could dictate cell fate. This topic is nicely reviewed by Cooper et al. in their manuscript.

Characterization of yeast cell death pathways has already provided relevant insights on higher eukaryotic cell's decision to live or die but may also reveal specific molecular components that might be used in anti-fungal therapy. Petitjean et al. provided evidence that Trehalose-6P Synthase (Tps1) acts as a pro-survival factor during growth, chronological aging, and apoptotic stress, independently of its catalytic activity. Since Tps1p is present in fungi but absent in mammals, it emerges as an attractive molecular target to selectively eliminate fungi, namely pathogenic species of *Candida* and *Aspergillus*, without causing major secondary negative effects in Humans.

Yeast cells have been extensively exploited to select modulators of regulated cell death. In their manuscript, Thevissen and co-workers further explored the increased tolerance to apoptosis-inducing agents conferred by the plant-derived decapeptide OSIP108 in both yeast and human cells. By using a yeast cisplatin-based screening setup as a model to understand the survival-promoting nature of the OSIP108 peptide, they showed this activity can be significantly improved by single amino acid substitutions. These findings further support the potential of the OSIP108 peptide as a promising therapeutic agent.

Giannattasio's team expressed the Carnation Italian ringspot virus (CIRV) p36 in yeast cells and evaluated cell survival and death. They showed that although CIRV p36 *per se* does not cause cell death in yeast cells it modulates the nature of acetic acid-induced cell death by increasing the number of cells dying by necrosis. This work proved yeast as an invaluable model organism to address mechanisms of cell death modulation by virus.

Yeast has been exploited for more than 50 years as a cellular model to study molecular aspects of aging, a paradigm of natural cell death. Many advances on aging research have been obtained by studies on the two yeast-aging models, the replicative and the chronological lifespan. Kaeberlein and co-workers provided us a critical review on the main advantages and limitations of the microfluidic technologies. These technologies allow monitoring different cellular physiologic parameters during the entire lifespan and constitute powerful tools to advance the understanding of molecular aging.

Vai and co-workers show that nicotinamide (NAM)-supplemented cells phenocopy the long-lived *SIR2* deficient mutants during chronological aging both in exhausted medium and under extreme caloric restriction. They demonstrate that this

is due to inhibition of Sir2-mediated deacetylation of Pck1, which is linked to higher glyoxylate/gluconeogenesis flux and lower non-phosphorylating respiration, as observed in the mutant cells. Also, the low burden of superoxide anions together with these metabolic changes enhances chronological longevity upon NAM supplementation. This study provides new clues to the development of pharmacological therapies based on the modulation of sirtuin activity with potential impact on health-span extension. Keeping on the same thematic of cell signalling during chronological aging, Guedes and co-authors addressed the effect of caloric restriction (CR) on the alpha-synuclein toxicity in aged yeast cells. They found that the CR protective effect was achieved through the control of the opposite roles of Tor1 and Sir2 on autophagy, which results in homeostatic levels of this process. This finding provides clues to the design of new therapeutic strategies for intervention in synucleinopathies and for the understanding of cellular aging.

In line with Guedes's manuscript on the yeast model for synucleinopathies, this special issue also comprises two important revisions on yeast models to address molecular pathogenesis and therapeutic targets of neurodegenerative diseases. Franssens and colleagues from the Winderickx lab were pioneer on the exploitation of "humanized yeast" and provide a comprehensive overview on the current set of concepts on the use of yeast models for Hunt-

ington's, Parkinson's and Alzheimer's diseases. These authors also call our attention to the potential of the fission yeast *Schizosaccharomyces pombe* to address molecular aspects associated with neurodegenerative diseases. Further complementing this topic, Cammue and co-workers highlighted in their review how the high conservation of regulated cell death mechanisms between yeast and mammalian cells might be used for the screening of novel survival-promoting drugs applicable to treat degenerative diseases.

The manuscripts gathered in this special issue of Mechanisms of Ageing and Development address complex questions on cell survival and death decisions in the yeast model, which has been strongly contributing to the advance of knowledge in this topic. Outwardly, it is possible to anticipate that yeast certainly will continue to enrich this fruitful and important area of research for many years to come.

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