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Oxidative stress and aging: Learning from yeast lessons

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ABSTRACT

The yeast *Saccharomyces cerevisiae* has played a vital role in the understanding of the molecular basis of aging and the relationship of aging process with oxidative stress (non-homeostatic accumulation of Reactive Oxygen Species, ROS). The mammalian and yeast antioxidant responses are similar and over 25 % of human-degenerative disease related genes have close homologues in yeast. The reduced genetic redundancy of yeast facilitates visualization of the effect of a deleted or mutated gene. By manipulating growth conditions, yeast cells can survive only fermenting (low ROS levels) or respiring (increased ROS levels), which facilitates the elucidation of the mechanisms involved with acquisition of tolerance to oxidative stress. Furthermore, the yeast databases are the most complete of all eukaryotic models. In this work, we highlight the value of *S. cerevisiae* as a model to investigate the oxidative stress response and its potential impact on aging and age-related diseases.

1. Introduction

Oxygen is required for aerobic life but may also play a crucial role in the aging process. According to the oxidative stress theory of aging, aging and age-associated diseases are associated with the damage caused by reactive oxygen species, ROS, to cellular constituents (Finkel and Holbrook, 2000).

The majority of ROS production occurs in the electron transport chain (ETC) of the mitochondria (Sheu et al., 2006). In this process, one molecule of oxygen receives four electrons being reduced to water; however, throughout the process, some of the electrons leak prematurely from electrons carriers to oxygen yielding ROS (Murphy, 2009). As electrons are sequentially transferred from complex I or complex II to complex III and then to complex IV, protons are translocated from the mitochondrial matrix to intermembrane space creating an electrochemical gradient, which is used as energy to ATP synthesis by ATP synthase. During this transport, electrons can be directly transferred to oxygen to generate superoxide (single-electron transfer) or hydrogen peroxide (pair-electron transfer), mainly at complex I, II and III, which use ubiquinone as acceptor (Brand, 2016). Superoxide remains within the compartment in which is generated, because it is unable to cross membranes. Superoxide is rapidly converted to hydrogen peroxide by the enzyme superoxide dismutase (SOD) (Herrero et al., 2008). Superoxide can also undergo spontaneous dismutation, although at a slower rate (Abreu and Cabelli, 2010). Contrary to superoxide, peroxide can cross membranes and be fully reduced to water by catalases or peroxidases. Alternatively, peroxide can be partially reduced to hydroxyl radical, the most reactive and dangerous radical, a reaction which requires the presence of reduced iron or cupper (Herrero et al., 2008). Hydroxyl radical can also be generated when superoxide reacts with nitric oxide, producing another highly reactive and dangerous radical, nitrogen dioxide (Sheu et al., 2006).

The oxygen consumption rate depends on the organism and its physiological condition. Human body extracts around 2500 calories from food by consuming around one hundred millions molecules of oxygen per cell per minute (Wagner et al., 2011). It is estimated that 0.01 % of all oxygen consumed is converted to ROS in the skeletal muscle during exercise (at rest, this percentage is 10-fold higher); thus, 10^4–10^5 molecules of ROS are formed per cell each minute (Goncalves et al., 2015). In face of these high ROS production rates, which increase the risk of hydroxyl radical formation, against which there is no defense, the cellular antioxidant system is very efficient: i) the proportion between antioxidant enzyme and its substrate is inverted (there is much more catalyst than substrate);

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ii) the rate of the antioxidant enzyme-catalysed reaction is only limited by diffusion (kcat/Km in the order of 10^8–10^9 M^{-1} s^{-1}) (Chelikani et al., 2004; Abreu and Cabelli, 2010).

The efficient and sophisticated antioxidant defense system counteracts and regulates overall ROS levels to maintain physiological homeostasis (Fig 1A). Lowering ROS levels below the homeostatic set point impairs the physiological role of ROS in some cellular processes, such as induction of antioxidant defense, cell proliferation, and host defense. On the other hand, increased ROS levels are also detrimental. ROS are able to damage all the cell building blocks, such as DNA, lipids, and proteins, leading to membrane damage, loss of organelle functions, reduction in metabolic efficiency, chromatid breaks and mutations (Schieber and Chandel, 2014). Fig 1B outlines the impact of ROS levels on cellular physiology.

According to oxidative stress theory of aging, first proposed in 1954, aging is correlated to the accumulation of cellular damages triggered by ROS produced by normal cell metabolism (Harman, 2006). Therefore, throughout the aging process, antioxidants decreased, increasing oxidative damage and, consequently, the chance of disease and death. Oxidative stress has been implicated in the progression of age-related diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) (Barnham et al., 2004b). Several data support the oxidative stress theory of aging (Harman, 2006; Viña et al., 2013). In 2011, a review was published which summarized the main data obtained from different studies that evaluated the oxidative stress indexes in healthy individuals related to age (Del Valle, 2011). In those studies, hundreds of volunteers from diverse nationalities were analyzed, and healthy individuals were divided according to their ages, confirming the oxidative stress theory of aging. However, some studies presented conflicting and contradictory results concerning the level of some antioxidants found in older people. In the last years, genetically modified animals were obtained to test the oxidative stress theory of aging. Some studies found that the overexpression of antioxidant enzymes extends lifespan, corroborating the theory, but other works put it in doubt by showing that increased ROS levels increase longevity (López-Otín et al., 2013; Viña et al., 2013). Taken into consideration the role of ROS in the response to stress condition, which is crucial for cell survival, it is possible to harmonize both interpretations (Reczek and Chandel, 2015). Mild concentrations of ROS are necessary to induce antioxidant defense, increasing cell protection and longevity. However, if the level of ROS exceeds the protective capacity of the antioxidants,

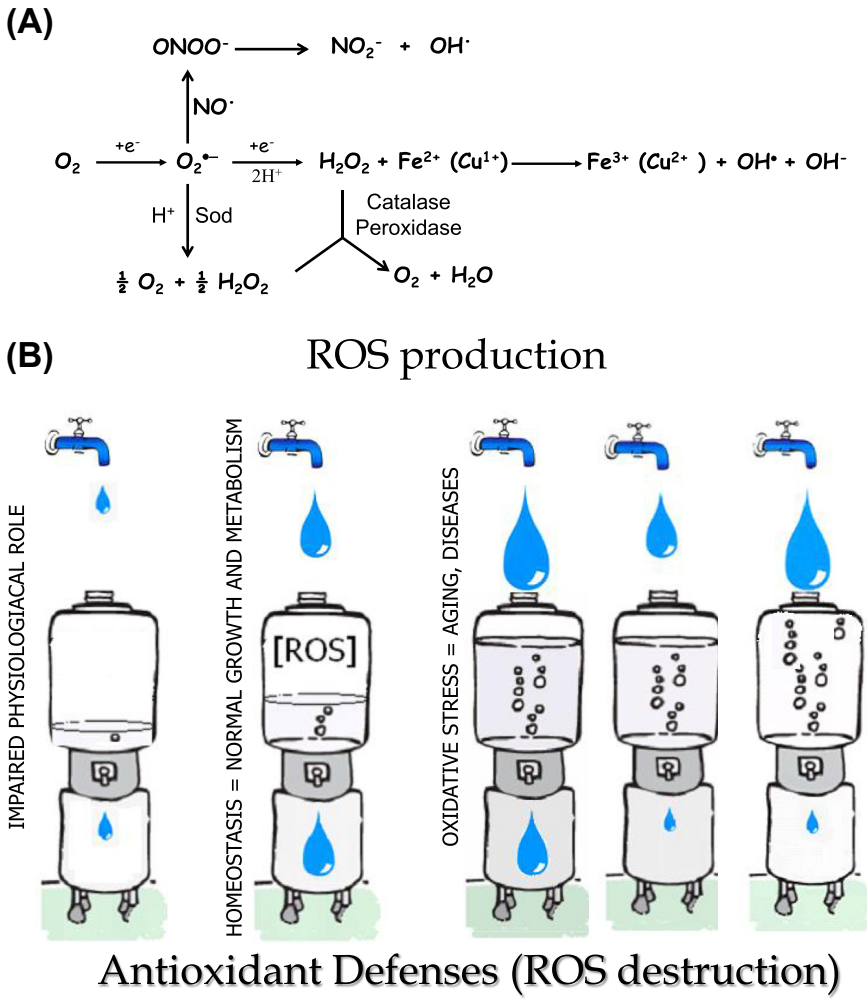

Fig 1. (A) ROS production, as a result of normal metabolism, and antioxidant enzymes that counteract and regulate overall ROS levels to maintain physiological homeostasis. (B) Reduced ROS levels, which can be achieved by a low ROS production (for example, during fermentative metabolism), are detrimental due to impaired physiological process, such as the induction of antioxidant defense system. As a consequence, cells are more sensitive to increased levels of oxidants, accelerating aging and increasing the chances of diseases. On the other hand, increased ROS levels (oxidative stress) are also deleterious. An oxidative stress occurs when the production of ROS overcome the antioxidant defense, which can be achieved by an increase in ROS production, a decrease in the antioxidant activity, or both.

oxidative damage will take place, accelerating aging and increasing the chance of diseases.

The molecular mechanisms of the oxidative stress response and the role of ROS in the biology of aging and in the development of age-related diseases have not yet been fully understood. The use of simple models such as the microorganism *Saccharomyces cerevisiae* has helped with the elucidation of these questions. Studies using this yeast have already contributed to the understanding of basic cellular and molecular processes. In 1996, *S. cerevisiae* had its genome fully sequenced and published. Since then, the extensive functional characterization of its genome (around 90 %) along with the huge genetic conservation with humans have triggered a series of new works which humanized the yeast (Khurana and Lindquist, 2010; Engel et al., 2013; Kachroo et al., 2015). Corroborating this evidence is the fact that between 2001 and 2016, five Nobel Prize winners (in Table 1) have used yeast as experimental model. Thus, in addition of being used in ancient biotechnological processes, such as alcoholic fermentation and backing, yeasts are currently explored for the production of therapeutic products, such as human hormones (insulin, insulin analogues, somatotropin, glucagon), vaccines (hepatitis B virus surface antigen and virus-like particles of protein L1 of human papillomavirus), human growth factors (IGF1, NGF, EGF) and human blood proteins (hemoglobin, factors VIII and XIII, antithrombin III, serum albumin albumin) (Ferrer-Miralles et al., 2009).

S. cerevisiae has some interesting characteristics that explain its extensive use as an experimental eukaryotic cell model or as a platform to produce recombinant proteins. Besides being non-pathogenic and classified as GRAS (Generally Recognized as Safe) by Food and Drug Administration (FDA), it has a short generation time (1.5–3 h) and grows in a highly reproducible and genetically stable way. In addition, it is amenable to genetic modifications by recombinant DNA technology or classical genetic manipulations. Other advantages for choosing *S. cerevisiae* as model are: (i) the ease in obtaining mutants from commercial collections of yeast strains for studies of functional genomics, subcellular protein localization, ant protein–protein interaction; (ii) the availability of public databases, such as Saccharomyces Genome Database (SGD), which organize and permanently actualize data obtained from omics studies, such as transcriptomics, proteomics, metabolomics, interactomics (protein–protein interactions), and locasomics (protein localization) (Laurent et al., 2016).

Studies of budding yeast have made immense contributions to our understanding of the aging process and age related-diseases (Kaeberlein, 2010). It is possible to study both chronological and replicative ageing using *S. cerevisiae* (Oliveira et al., 2017). Chronological aging is defined by how long a cell can survive in a non-dividing state. Throughout aging, cellular and molecular damages accumulate. Chronological lifespan is measured by culturing cells in non-proliferating conditions and then determining viability over time. Replicative ageing is defined by the number of daughter cells produced by a mother cell before senescence. Damages are asymmetrically inherited by the mother cell and removed from the daughter cell. Replicative lifespan (RLS) is measured by physical removal of daughter cells, which are easily distinguished from mother cells.

Several pathways involved in degenerative diseases are conserved in yeast, such as protein folding and degradation, autophagy, vesicular trafficking, lysosomal and peroxisomal role, and apoptosis (Tenreiro and Outeiro, 2010). Moreover, 17 % of the *S. cerevisiae* genes (approximately 1000 genes) are members of orthologous genes families associated with several human diseases (Botstein and Fink, 2011).

The oxidative stress response of *S. cerevisiae* is similar to that of mammals, including the sites of ROS formation in the ETC and the main antioxidant enzymes (Herrero et al., 2008). Yeast lacks complex I, but has three rotenone-insensitive NADH-ubiquinone oxidoreductase, Ndi1, Nde1, and Nde2, located at the mitochondrial inner membrane space. Mitochondrial matrix NADH is oxidized by the internal Ndi1, while Nde1 and Nde2, with their active sites facing the mitochondrial intermembrane space, oxide the external NADH. Like complex I of mammals, Nde1 and Nde2 are important sources of ROS in the *S. cerevisiae* ETC (Fang and Beattie, 2003).

By manipulating growth conditions, yeast cells can survive only fermenting or respiring (Kayikci and Nielsen 2015). At high concentrations of glucose (above 70 mM), *S. cerevisiae* can only undergo fermentation; therefore, ROS levels are reduced. As consequence, intracellular antioxidant defense system is repressed and cells are highly sensitive to oxidative stress. However, yeast cells can adapt to severe oxidative stress if exposed to external antioxidants or moderate concentrations of oxidants (Fernandes et al., 2007). Thus, this strategy helps to processes involved with acquisition of tolerance to oxidative stress and its correlation with degenerative processes. In other experimental models, such as mammal cells, which depend on respiration to obtain energy, the correlation ROS-aging is more difficult to analyze.

S. cerevisiae is only able to respire when growing in non-repressor carbon sources, such as glycerol and ethanol. Thus by plating yeast cells in media containing glucose or glycerol, we are able to determine the frequency of respire-deficient mutant cells, known as petite (Mannarino et al., 2008). Petites are unable to respire because they possess some mitochondrial dysfunction, a process highly implicated with degenerative diseases (Barnham et al., 2004a; López-Otín et al., 2013). On the other hand, since

Table 1
Nobel prizes for yeast! Nobel Prizes awarded for Physiology or Medicine and Chemistry which used *S. cerevisiae* as eukaryotic cell model.

Year	Nobel prize in	Laureates	Rationale
1907	Chemistry	E. Buchner	“for his biochemical researches and his discovery of cell-free fermentation”.
1929	Chemistry	A. Harden & H. von Euler-Chelpin	“for their investigations on the fermentation of sugar and fermentative enzymes”
1968	Physiology or Medicine	R. Holley, H. Khorana & M. Nirenberg	“for their interpretation of the genetic code and its function in protein synthesis”. The first primary structural determination of a tRNA, that of yeast alanine tRNA by R. Holley's group at Cornell University
1999	Physiology or Medicine	G. Blobel	“for the discovery that proteins have intrinsic signals that govern their transport and localization in the cell”.
2001	Physiology or Medicine	L. Hartwell, P. Nurse & T.Hunt	Hartwell discovered genes that control the cell cycle in *S. cerevisiae*
2004	Chemistry	A. Ciechanover, A. Hershko & I. Rose	Ciechanover used yeast to elucidate the ubiquitin-mediated protein degradation
2006	Chemistry	R. Kornberg	“for his studies of the molecular basis of eukaryotic transcription”.
2009	Physiology or Medicine	E. Blackburn, C. Greider & J. Szostak	Szostak studied the role of telomere elongation in yeast senescence
2013	Physiology or Medicine	J. Rothman, R. Schekman & T. Südhof	Schekman used yeast to study the mechanisms of vesicle traffic
2016	Physiology or Medicine	Y. Ohsumi	“for his discoveries of mechanisms for autophagy”.

S. cerevisiae is not exclusively dependent on respiration to survive, mutations that result in mitochondrial dysfunction can be investigated in this model organism (De Carvalho et al., 2017).

This review focuses on the contribution of yeast in understanding the binomial oxidative stress-molecular mechanisms involved in age-related pathologies, such as neurodegenerative diseases and cancer.

2. Neurodegenerative diseases

2.1. Cellular processes and aggregation in yeast models

Protein misfolding and aggregation are widely recognized as key features of age-related illness, specifically neurodegenerative diseases (Hartl et al., 2011; Saez and Vilchez, 2014). In recent years, the budding yeast *S. cerevisisae* has provided important general insights for deciphering the basis of neurodegeneration, underlying protein misfolding (Shrestha and Megeney, 2015). Furthermore, yeast models of neurodegeneration have identified cellular factors that modulate aggregation and subsequent toxicity of proteins associated with PD (Outeiro, 2003), AD (Vandebroek et al., 2005; Caine et al., 2007), Huntington's Disease (HD) (Krobitsch and Lindquist, 2000; Willingham, 2003) and ALS (Johnson et al., 2009; Bastow et al., 2016). These proteins include fibrillar α-synuclein (α-Syn), which accumulates in proteinaceous inclusions, known as Lewy bodies observed in familial and sporadic cases of PD (Spillantini et al., 1997). The AD pathological hallmarks include the formation of extracellular plaques structures containing amyloid-β (Aβ) as well as intracellular buildup of neurofibrillary tangles of hyperphosphorylated tau protein (Fruhmann et al., 2017). Likewise, HD is characterized by the presence of intracellular cytotoxic aggregation of huntingtin protein (Htt) containing polyglutamine (polyQ) expansions (Ross and Poirier, 2004; Novak and Tabrizi, 2010). The accumulation of cytoplasmic aggregates of Cu,Zn-superoxide dismutase (Sod1), the RNA-binding proteins TDP-43 and FUS, has been implicated in ALS affected patients (Rosen et al., 1993; Neumann et al., 2006; Vance et al., 2009). The abnormal structures formed by these different protein species have also been implicated in impairing the proteasomal functionality as well as the expression of proteins involved in proteostasis (Tyedmers et al., 2010; Shrestha and Megeney, 2015). Because the protein misfolding, quality control, and degradation machineries as well as oxidative stress response are remarkably well conversed across eucaryotes (Tenreiro et al., 2013; Oliveira et al., 2017), yeast has emerged as a robust and tractable organism to model proteostasis and oxidative modifications in neurodegenerative diseases.

The mechanisms underlying α-Syn dysfunction in PD as well as in other disorders termed synucleinopathies have been successfully studied in yeast models based on the heterologous expression of human α-Syn (Outeiro, 2003). The first study conducted in yeast models of PD showed that α-Syn toxicity led to the formation of intracellular inclusions and the expression of α-Syn resulted in dose-dependent cytotoxicity (Outeiro, 2003). In this study, the intracellular localization was investigated in yeast cells by expressing the fluorescently labeled wild type (WT) and mutant A53T α-Syn. Both WT and A53T α-Syn were directed to the plasma membrane at lower expression levels, and they were able to accumulate into cytoplasmic inclusions upon increased expression levels. Moreover, α-Syn expression in yeast established dysfunction in several cellular processes promoting lipid accumulation and affecting vesicular trafficking as well as the proteostasis machinery (Outeiro, 2003; Lázaro et al., 2017). Extensive evidences on the involvement of the protein quality control systems, response to mitochondrial damages and regulation of vacuolar transport in neurodegeneration came from studies of mutations in several genes associated with PD (eg. DJ-1, Parkin, Pink1, ATP13A2) as well as using yeast humanized models (Menezes et al., 2015). Hsp31, Hsp32, Hsp33, and Hsp34 are examples of Heat shock proteins highly conserved in yeast which belong to DJ-1 family. It was found that human DJ-1 and the yeast orthologues physically interacted with α-Syn, ameliorating the α-Syn induced toxicity and reducing α-Syn aggregation in yeast cells (Zondler et al., 2014). Human Parkin expressed in yeast has promoted chronological longevity and oxidative stress resistance, which appeared to be dependent on mitochondrial function (Pereira et al., 2015). Yeast models were also used to confirm the relevance of Pink1-dependent phosphorylation of ubiquitin, in the activation of Parkin (Koyano et al., 2014). *YPK9* gene is the yeast orthologue of lysosomal P-type ATPase ATP13A2, and the mutated protein can cause early-onset PD (Gitler et al., 2009). Studies performed in yeast cells showed *YPK9* suppressed the α-Syn toxicity and that this benefit depends on the vacuolar localization and ATPase activity of Vps35. In addition, the enhanced α-Syn toxicity in *vps35*Δ yeast strain corroborated the increase in α-Syn inclusion accumulation in the vacuole (Dhungel et al. 2015).

The uses of AD humanized yeast models have provided powerful new approaches to help understand the molecular mechanisms underlying tau and Aβ toxicity. Using *S. cerevisiae* to study the mechanisms and phenotypical influence of expression of alpha-synuclein as well as the coexpression of protein tau, Zabrocki et al., 2005 showed that both proteins are synergistically toxic in yeast cells, as observed by inhibition of proliferation (Zabrocki et al., 2005). It has been shown that the human phosphorylated Tau-3R and 4R isoforms expressed in yeast assumed a pathological conformation and aggregated (Vandebroek et al., 2005). In addition to post-translational modifications and oligomerization/aggregation, oxidative stress is also involved in AD pathogenesis; however, the interaction between them are still unclear. In yeast, oxidative stress and mitochondrial dysfunction, produced by the addition of Fe^{2+} ions, enhanced human tau aggregation independent of phosphorylation (Vanhelmont et al., 2010). Although Aβ aggregation is associated with the formation of extracellular amyloid plaques in AD patients, Aβ species also accumulate inside the cell, including intracellular multivesicular bodies (Almeida, 2006), lysosomes, or other vesicular compartments (Nixon, 2007; D'Angelo et al., 2013). The creation of the first yeast model to study AD in yeast cells by the expression of GFP-fused Aβ served as an important basis to investigate the toxic effects of Aβ on these cellular processes in yeast cells (Caine et al., 2007). Further, by using a By4741 based yeast system expressing Aβ-link-GFP construct, D'Angelo et al., 2013 established a system in which Aβ enters the secretory pathway and goes to the plasma membrane becoming toxic to the cells (D'Angelo et al., 2013). Using this model, the authors were able to define intracellular traffic pathways as a necessary process for the generation of toxic species in yeast cells.

Yeast models to study HD have recapitulated the polyQ length-dependent aggregation and toxicity by expressing different versions of human Htt protein. Moreover, many other mechanisms involved in the mutant Htt-induced toxicity have been identified from yeast models, such as the modulation of specific molecular chaperones (eg. Hsp104, Sis1 and Ssa1/2), the propagation of endogenous prions, and the autophagic clearance of polyQ protein in yeast (Krobitsch and Lindquist, 2000; Meriin et al., 2002). It has also been successfully established that aggregation of mutant Htt in yeast affects endocytosis, cell cycle progression, proteolysis and mitochondrial function (Meriin et al., 2007; Bocharova et al., 2008; Duennwald and Lindquist, 2008; Tauber et al., 2011; Kochneva-Pervukhova et al., 2012). Recently, the beneficial effect of the protein refolding machinery in inhibiting the aggregation of the mutant Htt 103Q was demonstrated as result of the activation of

trehalose synthetic enzyme, trehalose-6-phosphate synthase 1 and Hsp104 in heat shocked *S. cerevisiae* cells (Saleh et al., 2014).

Since oxidative modifications to proteins increase during aging, it had been proposed that oxidation of Sod1 mutants associated to the familial form of ALS (FALS) may trigger their misfolding and aggregation (Dal Vechio et al., 2014; Petrov et al., 2016). By using chronologically aged yeast cells, it was shown that the expression of A4V mutation on human Sod1 as well as the absence of the antioxidant glutathione (GSH) affected human Sod1 activation and increased oxidative damage compared to the WT isoform. This study indicated GSH as a prominent target in the molecular mechanism of FALS during aging (Brasil et al., 2013). In addition, studies using a yeast background to investigate FALS found that pathogenic mutations in TDP-43 protein promote its aggregation and toxicity (Johnson et al., 2009). The inclusions readily formed by TDP-43 protein in yeast models showed similar effects in higher eukaryotic models (Figley and Gitler, 2013) and were structurally identical to aggregates in degenerating neurons of patients with ALS (Johnson et al., 2008). Such studies suggest the yeast model remains an ideal platform to study the cellular processes of several aggregation-prone proteins that characterize neurodegeneration.

2.2. Mitochondrial dysfunction, oxidative biomarkers and antioxidant molecules

A large number of studies demonstrate that mitochondrial dysfunction and oxidative stress are hallmarks of PD (Sharma et al., 2006; Vila et al., 2008; Federico et al., 2012). As mentioned before, the accumulation of α-syn protein is one of the main causes of PD. *In vitro* experiments showed that α-syn reversibly blocks the largest flow channel of metabolites in and out of mitochondria (VDAC), located on the mitochondrial outer membrane (Rostovtseva et al., 2015). The same work, using a yeast model for PD, demonstrated that the α-syn toxicity is VDAC dependent. On the other hand, the autosomal recessive form of PD is associated with mutations in the Parkin protein, an E3 ubiquitin ligase. Parkin and Pink1 are associated with mitochondrial autophagy process in response to stress (Shiba-Fukushima et al., 2017). Pereira et al (2015) used a yeast model to study the human Parkin protein, and noted that Parkin was able to increase the chronological lifespan and resistance to oxidative stress of yeast cells. In response to stress with hydrogen peroxide, the Parkin protein, initially expressed in the cytosol, is translocated to the mitochondria, promoting greater degradation.

In AD, the Aβ accumulates intra and mainly extracellularly, as a result of amyloid precursor protein (APP) cleavage (Deyts et al., 2016). In 2011, a yeast model was created for studying amyloid toxicity, and in order to establish the relationship between Aβ toxicity, endocytosis and risk factors of AD (Treusch et al., 2011). Yeast cells were transfected with a multicopy plasmid containing Aβ1-42 amino acid sequence (driven to the secretory pathway) whose expression was controlled by the galactose-inducible promoter. This construction allowed identification of a series of Aβ toxicity modifiers, involved either in endocytosis or cytoskeleton. Using a similar model, Chen and Petranovic (2015) observed that yeast cells which produce Aβ constitutively, and directed to the secretory pathway, have decreased growth and respiratory rates, increased oxidative stress, and markers of mitochondrial dysfunction. More recently, França et al. (2017) demonstrated that mitochondrial dysfunction and, consequently, ROS increase occurs due to a change in the activities of complexes III and IV in the electron transport chain (ETC). Furthermore, to minimize the increase in intracellular oxidation, a series of cellular responses are triggered. One of these responses was the signaling transmitted to the nucleus to regulate the increase of the expression of enzymes like aconitase (Aco1), catalases (Cta1 and Ctt1) and superoxide dismutases (Sod1 and Sod2). In the mitochondria, Cta1 and Sod2 demonstrated to operate jointly in the maintenance of redox homeostasis and mitochondria integrity.

The Sod1 isoform of superoxide dismutase also plays an important role in ALS. Martins and English (2014) used yeast cells as a model for non-dividing motor neurons and observed that the protein misfolding mechanisms that give rise to sporadic ALS (SALS) are triggered by oxidative damage in the wild-type Sod1. Recently, Bastow et al. (2016) used yeast to demonstrate that the toxic effect of Sod1 instability promotes senescence because it avoids vacuole acidification and impairs metabolic regulation, and not because it is related to loss of mitochondrial function or ROS increase.

Despite the advances made in the research on neurodegenerative disorders, they have no cure and therapeutics needs information about the mechanisms involved in the process, which are still poor elucidated. The neurotoxicity exhibited in a series of disorders is associated with increased levels of oligomers and fibers in the brain. Hence, a number of compounds have been studied in order to find toxicity suppressors by disaggregation and/or oxidative stress reduction, and yeast has proven to be an excellent model for this type of analysis.

Polyphenols represent the most abundant class of antioxidants in the human diet, being widely found in different types of foods. Therefore, in the past several years, a great number of studies have demonstrated their beneficial effects on neurodegenerative disorders such as AD and PD (Moosavi et al., 2016). Recently, a family of 21 polyphenolic compounds, consisting of those found naturally in leaves of salvia, and some of their analogues, were synthesized and subsequently screened for their activity against the Aβ peptide in yeast cells, which found that they were able to revert the toxicity generated by the peptide (Porzoor et al., 2015). The same work observed that 14 of these compounds were able to significantly decrease fluorescence in yeast cells transformed with Aβ fused to GFP. In another work, polyphenols from *Corema Album* leaves were able to reduce the formation of α-syn inclusions, ROS levels, and consequently, cytotoxicity in yeast cells (Macedo et al., 2015).

3. Mitochondrial dysfunction in cancer and yeast cells

Mutations in mtDNA and impairment of mitochondrial function arise as an inevitable consequence of aging and oxidative stress. Mutations in nuclear and mitochondrial genes involved in the oxidative phosphorylation (OXPHOS) were reported to play a significant role in the development of tumorigenesis (Chandra and Singh, 2011), and mitochondrial dysfunction is being considered an important hallmark of cancer cells (Modica-napolitano and Singh, 2004; Rossignol et al., 2009). The damage to mitochondrial function and structure can be caused by ROS generated during respiration. The progressive loss of mitochondria respiratory capacity has been linked to the metabolic and genetic transformation observed in cancer cells (Seyfried, 2015).

Mitochondrial DNA mutations and changes in their content have been increasingly identified in various types of cancer and correlated to malignancy (Chandra and Singh, 2011). Mutations in mtDNA D-loop region have been reported as an independent molecular prognostic indicator in breast cancer (Mantripragada et al., 2008).

mtDNA is small, lacks introns, has a limited DNA repair capability, lacks protective histones and relies on a single control region (D-loop) to control replication and transcription of its genes (Chandra and Singh, 2011). As mitochondrial biomolecules are directly exposed to ROS generated during cell respiration, mitochondria are highly susceptible to oxidative damage. ROS generated during the ETC can damage mitochondrial lipids (e.g., lipid

peroxidation), causing changes in membrane fluidity and permeability; can oxidize proteins, causing loss of function and metabolic burden to the cell; and direct damage mtDNA, which causes progressive defects in the expression of the OXPHOS components coded by mtDNA. ROS damage to mtDNA can also impair the replicative capacity of mtDNA or even interfere with fusion and fission events that are necessary for mitochondrial remodelling. The cumulative generation of ROS progressively damages mitochondrial structure and function; as a consequence, the respiratory capacity of the cell becomes impaired (Van et al., 2003).

Given the importance of mtDNA for the proper expression and constitution of the OXPHOS system, any mutations in its genetic content will have a huge impact on the respiratory capacity of the cell. To keep the energetic level and produce metabolic intermediates to maintain its proper metabolic function the cell must express adaptive responses to mitochondrial dysfunction. These responses include genetic and metabolic adaptations that act to rearrange primary biochemical pathways and intracellular responses to maintain cell viability in the presence of a respiratory dysfunction (Singh, 2004; Seyfried, 2015).

The progressive oxidative damage is a well-known effect of aging, but the specific oxidative damage to mitochondria has been gaining increase attention by the scientific community and is being considered by some authors one of the most important factors in the malignant metabolic transformation of the cell observed in cancers (Seyfried, 2015). *S. cerevisiae* is an interesting model to study cancer as a mitochondrial metabolic disease, because this yeast is able to survive without functional mitochondria and even in the total absence of mtDNA, enabling study about the effects of respiratory impairment on the genomic and metabolic profile of the cell. Yeast cells that contain wild-type mtDNA (referred to as *rho*$^{+}$) are able to perform the OXPHOS and metabolize non-fermentable carbon sources. If there are mutations in mtDNA (*rho*$^{-}$ cell) or a complete loss of mtDNA (*rho*^{0} cell), the cells are unable to express functional mtDNA-encoded subunits of the ETC and/or OXPHOS, thus they become respiratory-deficient and are unable to metabolize non-fermentable carbon sources (Dirick et al., 2014). These cells, usually referred to as *petite*, because of their small colony size, are only capable of growing on fermentable carbon sources (such as glucose), which are a substrate for glycolysis. The *petite* phenotype can arise as a consequence of mtDNA (cytoplasmic *petite*) or nDNA (nuclear *petite*) mutations that compromise the OXPHOS system. The relative simplicity in identifying and isolating *petite* mutants in *S. cerevisiae* allowed researchers to study the effects of mtDNA depletion and respiratory damage on the metabolic and gene expression profile of the cell (Merz and Westermann, 2009), helping identify fundamental gene-products that are essential for mitochondrial function. The investigation of mitochondrial processes in yeast provided important data for the comprehension of mitochondrial dynamics in human cells (Kuzmenko et al., 2016), mostly because of the similarity between human and yeast mtDNA biochemistry (Smith and Snyder, 2006). For example, the first gene encoding a mtDNA polymerase was discovered in yeast (MIP1) (Foury, 1989).

S. cerevisiae has been used as a model organism to investigate not only mitochondrial dynamics, function and oxidative stress, but also the dynamics of the metabolic adaptation to mitochondrial damage. *S. cerevisiae* studies showed that there is a causal relationship between mtDNA damage and genomic instability in the nucleus (Rasmussen et al., 2003; Doudican et al., 2005). These studies provide important data to support that mitochondrial oxidative damage caused by ROS, associated with respiratory impairment, can cause genomic instability and direct mutations in the nucleus. The question raised by using yeast model in these experiments is whether mitochondrial damage can act as a driver cause in the malignant metabolic and genetic transformation observed in cancer cells. As ROS can damage mitochondria structure over time, could ROS play a central role in cancer development? This issue has been investigated and growing evidence supports direct damage by ROS to mtDNA is important for tumorigenic profile development (Sabharwal and Schumacker, 2014).

To cope with respiratory function impairment caused by progressive loss of mitochondrial function due to oxidative damage, the cell must be able to perform an adaptive response to reorganize cellular metabolism in order to obtain metabolite intermediates in the presence of an impaired TCA, ETC or OXPHOS. The first well characterized pathway that signals mitochondrial dysfunction to the nucleus in order to express and adaptive response was studied in *S. cerevisiae* and is referred to as retrograde pathway (RTG) (Butow and Avadhani, 2004; Da Cunha et al., 2015). Basically, the yeast protein Rtg2p senses variations in homeostatic signals from mitochondria that are related to respiratory dysfunction, which causes a cascade of events that culminates with translocation of the heterodimeric complex Rtg1-Rtg3p to the nucleus and activation of gene expression in response to the mitochondrial dysfunction. Some of the genes controlled by RTG response are required for activation of anaplerotic pathways and glyoxylate cycle, which provides precursors for the biosynthesis of tricarboxylic acid (TCA) cycle intermediates from acetate, even in the presence of a truncated TCA cycle due to mitochondrial dysfunction (Jazwinski, 2013). The retrograde pathway was also found to play a significant role in extending yeast chronological lifespan (Hashim et al., 2014) and promoting nuclear genome stability (Borghouts et al., 2004). The retrograde pathway is well known and characterized in the yeast model human cells also have a pathway that signals mitochondrial dysfunction and stress signals to the nucleus to express adaptive responses to respiratory impairment. One important effector of this response in human cells is the transcription factor NFκ-B, considered to have evolved from RTG-dependent retrograde pathway (Srinivasan et al., 2010), and is responsible for a wide spectrum of signalling, genetic and metabolic adaptations to stress, organelle dysfunction and aging (Hoesel and Schmid, 2013; Jing and Lee, 2014). Bioinformatics analysis has found a structural homology between mammalian Myc-Max heterodimer and yeast Rtg1-Rtg3 complex, which is responsible for the activation of gene expression in yeast retrograde pathway. The transcription factor c-Myc was found to be activated in human cells upon activation of the retrograde response. NFκ-B has two binding sites for Myc, a transcription factor found to be activated upon retrograde response, suggesting communication of these factors in the retrograde response pathway in human cells (Jazwinski, 2013). RTG pathway in yeast also plays an important role in oxidative response. Mutant cells, with an impaired RTG pathway, decrease in important antioxidant enzymes, such as catalase and glutathione peroxidase, making them more vulnerable to oxidative stress (Da Cunha et al., 2015).

ROS damage to mitochondria gradually increases with aging. As a consequence, the respiratory function of the cell is progressively impaired. In order to cope with the loss of respiratory function, the cell activates a retrograde pathway that signals the mitochondrial damage to the nucleus, activating the expression of a transient metabolic response to allow the cell to deal with the impaired respiration until the mitochondrial damage is repaired by other pathways, such as the mitocheckpoint (Singh et al., 2009). If the mitochondria function is restored, the cell returns to its homeostatic metabolic state. If mitochondria damage is severe and cannot be repaired, the retrograde response is persistent, which leads to a progressive shift in the metabolic profile of the cell and causes genome instability in yeast (Doudican et al., 2005). In human cells, this process culminates with the development of the tumour

metabolic profile, resistance to apoptosis, upregulation of oncogenes and nuclear genome instability (Singh, 2004).

S. cerevisiae has a variety of genes that are homologous to the proto-oncogenes of human cells, which allows the use of the yeast model to study how such genes control essential processes in the cell. For example, the glucose-induced repression of oxidative metabolism in yeast, referred to as catabolite repression or Crabtree effect, is regulated by oncogene homologues, such as RAS and SCH9 (Guaragnella et al., 2014). The yeast Crabtree effect and the Warburg effect of cancer cells are similar in terms of the metabolic outcome (Diaz-ruiz et al., 2009; Diaz-Ruiz et al., 2011; Natter and Kohlwein, 2013). In both cell types, there is a downregulation of oxidative metabolism and an enhancement of fermentation, despite the presence of oxygen. These changes cause a rearrangement of the oxidative profile of the cell. While the Warburg effect is considered an irreversible phenotype of cancer cells, *S. cerevisiae* Crabtree effect is a reversible phenotype, as the catabolic repression depends on high glucose concentration. These metabolic similarities indicate that *S. cerevisiae* is a useful model to study cancer cell metabolism and screen for metabolic-targeted drugs for antitumour therapy.

The yeast genes RAS1 and RAS2 are homologous to the RAS proto-oncogenes of the mammalian cells and were the first ones to be implicated in yeast longevity (Tamanoi, 2011). The convergence of the RAS pathway and the RTG pathway, through the regulatory function of Mks1p (Sekito, 2002), controls stress resistance and life span in yeast (Shama et al., 1998; Jazwinski, 1999). The SCH9 gene of *S. cerevisiae* codes for a protein kinase with a catalytic domain, which is very similar to that of the human Akt1, a known oncogene that promotes cellular growth and activates proliferation and survival pathways in cancer (Carpten et al., 2007). Sch9p plays an important role in glucose signalling in yeast (Diaz-Ruiz et al., 2011), regulating the expression of ETC genes (Lavoie and Whiteway, 2008), and is a central component that controls the metabolic shift from TCA cycle and respiration (oxidative metabolism) to Glycolysis (Wei et al., 2009).

In the absence of orthologs, *S. cerevisiae* usually have an analogous pathway, or the human gene can be studied by heterologous expression and the resulting phenotype can be evaluated (Tosato et al., 2012). The well-known p53 protein, which controls some cellular processes related to cellular growth and apoptosis (Farnebo et al., 2010) and is frequently found mutated in cancer cells, does not have a direct homologous in yeast. However, the effect of its expression in yeast can provide relevant information about the role performed by this protein in regulating fundamental cellular processes conserved among yeast and human cells. Yeast has been used to screen for toxic mutations of p53 (Inga and Resnick, 2001; Šmardová et al., 2005), to identify intracellular location and dynamics of this protein (Abdelmoula-Souissi et al., 2011) and even to find functional homologous proteins that are able to metabolically interact with p53 (Facchin et al., 2003).

3.1. Anti-cancer drugs

The causes of cancer are related to point mutations, activation of oncogene, inactivation of tumor suppressors and epigenetic changes (Wiedemann and Morgan, 1992; Gao Guangxun and Chen Liang, 2014). Epigenetic modifications throughout aging lead the cells to cancer transformation, changing essential epigenetics process, such as DNA methylation and histone modifications, which are essential for normal cellular development (Fraga et al., 2007). Growth signaling in *S. cerevisiae* and in higher eukaryotes may impact oxidative stress and age-related diseases, like cancer, stimulating DNA replication stress, which leads to DNA damage and genome instability (Dayan et al., 2017). Targeted therapy is applied in cancer drug design to interfere in a specific site (usually a protein) that plays an important role in tumor growth and progression (Sawyers, 2004).

Chemical genetics is the intervention in biological systems using small molecules, this technique employs protein-bindings, high-throughput screening and phenotypic methods, and have been developed in the pharmaceutical field (Spring, 2005). Chemical genetics will lead to better development of studies in new antitumor drugs (Spring, 2005). Currently, model organisms, with the biochemistry of cancer-like tumor cells, have been used to study the effect and design of new antitumor drugs (Gao Guangxun and Chen Liang, 2014). In this context, *S. cerevisiae* is a widely known and used model organism in the investigation of cellular processes due to yeast conserved genome and cellular biology (Khurana and Lindquist, 2010). The current trend in cancer treatment research is development of drugs with defined molecular targets (Sangmalee et al., 2012).

The antitumor effect of some anticancer drugs is due to the production of ROS (Lu, 2005). β-Lapachone (β-lap) is a known natural products isolated from *Tabebuia impetiginosa* and is a naphthoquinone that holds anticancer activities (Hussain and Green 2017). *S. cerevisiae* was used to investigate the mechanisms by which β-lap acts against cancer. Unlike other quinone drugs, β-lap cannot inactivate enzymes involved in cancer, like topoisomerase II. Toxicity caused by β-lap in yeast cell is mainly due to oxidative and environmental stresses, and it leads to cell death like necrosis process. This compound has already entered in phase I and II clinical trials against cancer (Ramos-Pérez et al., 2014). Quercetin has powerful anticancer effects but presents some limitations like it poor water solubility. However, 3,7-dihydroxy-2-[4-(2-chloro-1,4-naphthoquinone-3-yloxy)-3-hydroxyphenyl]-5-hydroxychromen-4-one (CHNQ) is a quercetin derivative naphthoquinone, which induces ROS production and autophagy in yeast cells. CHNQ can be suggested as chemotherapeutic drug, because it can guide tumor cell to death (Enayat et al., 2016).

S. cerevisiae has been used to investigate drugs that act on DNA topoisomerases, which are important targets of anticancer therapeutics (Harbury et al., 1992; Sangmalee et al., 2012). Topoisomerases can be divided in type I (Top1) and type II (Top2) enzymes. Top1 cleaves a single strand of a DNA double-strand to allow passage of a second strand between the DNA break, which is reattached. Camptothecin is a Top1 inhibitor indicated as a antitumor drug and has been tested in the budding yeast (Nitiss and Wang, 1988; Reid et al., 1998). Top2 is highly conserved, is essential during mitosis, and responsible for cleaving and rejoin duplex DNA (Reid et al., 1998). Top2 enzymes are also important in cell growth and proliferation, with an increased expression. Many drugs have been tested in *S. cerevisiae*. Salvacine is a diterpenoid with a quinone moiety synthetized from a natural product isolated from *Salvia prionitis lance*. When tested in *S. cerevisiae*, Salvacine targeted topoisomerase II, inducing intracellular ROS production and generating double-strand DNA breaks (Lu, 2005). Top2 poisons are drugs capable of increasing breaking complexes top2-DNA, converting the enzyme in a cellular toxin, which leads to cell death (Hammonds et al., 1998; McClendon and Osheroff, 2007). Etoposide, amsacrine, and doxorubicin can inhibit the link of the cleaved strand (Froelich-Ammon and Osheroff, 1995; Hammonds et al., 1998; Van Hille and Hill, 1998). The other Top2 poison activity tested in *S. cerevisiae* include Daunorubicin, Genistein, Actinomycin D, Distamycin A, TOP 53, Cisplatin, Camptothecin, mitoxantrone, Vinorelbine, Cytosine arabinoside, Podophyllotoxin, Epipodophyllotoxin, Colchicine, Suramin, Irinotecan, Azatoxin, Etopophos (Van Hille and Hill, 1998), Ellipticine (Reid et al., 1998; Van Hille and Hill, 1998), and bisdioxopiperazine compounds (Reid et al., 1998; Van Hille and Hill, 1998).

Inhibition of histone deacetylase and DNA methyltransferase, using drugs with epigenetic modulating activity, has become a therapeutic target against cancer and aging (Khan et al., 2016). SIR2 encodes an NAD+-dependent histone deacetylase in charge of the hypoacetylated state of histones in chromatin silencing (Imai et al., 2000; Moazed, 2001). In yeast, Sir2p act in transcriptional regulation, cell cycle progression, DNA-damage repair, stress response, and aging (Gartenberg, 2000; Rodriguez and Fraga, 2010). Sirtuins have a high level of conservation of the catalytic domain (Grozinger et al., 2001). Splitomicin inhibits Sir2p activity (Bedalov et al., 2001; Hirao et al., 2003) and can be a drug candidate in other deacetylases for treating cancer. Acetylation or deacetylation leads to a chromatin remodeling, which drives the availability and transcriptional ability of a gene. Mistarget of enzymes can lead to a pathological gene silencing that appears in cancer. Histone deacetylases inhibitors are a promising candidate to desing of new antitumor drugs (Wolffe, 2001). A3 and sirtinol were the most powerful inhibitors of human SIR2 tested in *S. cerevisiae* (Grozinger et al., 2001).

Methylthioadenosine phosphorylase (MTAP), an important enzyme in the methionine salvage pathway, is silenced in a variety of human cancers (Subhi et al., 2003; Kadariya et al., 2011). All human tissues express MTAP, so it is important to investigate compounds that are capable of inhibiting the growth of MTAP deficient cells (Kadariya et al., 2011). *S. cerevisiae* was used to screen compounds that were able to inhibit the growth of cells lacking MTAP, which showed that compounds containing a 1,3,4-thiadiazine ring enhanced growth inhibition in yeast and human cells deleted in MTAP (Kadariya et al., 2011). MTA is a by-product of polyamine metabolism. The limiting enzyme in polyamine synthesis is ornithine decarboxylase (ODC), and overexpression of ODC can be observed in different kinds of cancers (Subhi et al., 2003). 4-methylthio-2-oxobutanoic acid (MTOB), an Intermediary of MTAP pathway, is suggested as a negative regulator of polyamine metabolism, which justifies MTAP as a tumor suppressor (Subhi et al., 2003).

When *S. cerevisiae* does not have direct orthologous with human cells, these genes can be expressed in heterologous form to study their functions and mechanisms (Guaragnella et al., 2014). *S. cerevisiae* has been used to identify PARP inhibitors. Inhibition of PARP1 and PARP2 (Poly(ADP-ribose) polymerases) activity has potential anticancer drug activity (Perkins et al., 2001). These enzymes are activated in oxidative stress (Hocsak et al., 2017) involved in the DNA repair pathways DNA replication and error-repair is a critical component of cancer cell survival (Dziadkowiec et al., 2016). Cells with BRCA-1 and BRCA-2 mutations harbor a defect in homologous repair and seem to be highly vulnerable to the effects of PARP inhibition. Therefore, inhibition of PARP presents a potential anticancer drug activity (Dziadkowiec et al., 2016). *S. cerevisiae* has been used to screen and identify active inhibitors of mammalian PARF in biochemical assay and in yeast cell extracts (Perkins et al., 2001). Thiochromenone and benzothiazinone are new inhibitors that appears to have more selectivity to PARP1; on the other hand, phthalazine seems to be more selective to PARP2 (Perkins et al., 2001). Some available PARF inhibitors are already in phase III trial, and showed antitumor efficacy (Dziadkowiec et al., 2016).

S. cerevisiae can be used to study the mechanism of a drug action. Antitumor drugs that damage DNA are considered to interfere in chromosomal DNA replication; however, the molecular mechanisms are not known (Wang et al., 2001). It was shown in *S. cerevisiae* that Adozelesin, an anticancer drug, blocks replication fork progression and inhibits the activity of replication origin (Wang et al., 2001). Another way to use *S. cerevisiae* is to analyze the cellular mechanism of antitumor drugs resistance. Cisplatin is a famous anticancer drug that forms platinum-DNA adducts (Perez et al., 1998) and induces ROS production by a process independent of DNA damage signaling in *S. cerevisiae* (Marullo et al., 2013). Unfortunately, some patients presents cellular resistance against cisplatin, which limits its therapeutic potential (Perez et al., 1998). Nitrogen permease regulator 2 (NPR2) is a yeast gene responsible for the inhibition of TORC1 activity, by regulating the synthesis and the intake of glutamine as a nitrogen source (Laxman et al., 2014). Cells lacking Npr2 have faster proliferative rate, and these gene is a tumor suppressor (Laxman et al., 2014). Cells with deleted Npr2 are resistant to cisplatin and doxorubicin (Schenk et al., 2003). Ruthenium compounds belong to the most promising candidates of non-platinum metal complexes in cancer therapy, and include KP1019, a promising anticancer drug during cancer treatment. Research in *S. cerevisiae* demonstrated that K1019 targets histone proteins, interacting with histone 3 (H3), with important consequences for DNA damage responses and epigenetics (Singh et al., 2014).

Another way to use *S. cerevisiae* to study anticancer drugs is related to the delivery of nanoparticles (drugs) to tumor cells. Antitumor drugs, mainly composed of small interfering RNA (siRNA) and other nucleic acids, have some problems such as poor solubility and stability, unwanted toxicity, and inability to pass over cell membrane. Therefore, it is important to investigate the delivery of drugs to the target cells (Yoo et al., 2011). The lipid composition in cell membrane of *S. cerevisiae* is quite similar to the composition of mammal membranes (Weisman, 2003; Armstrong, 2010); therefore, the yeast vacuoles are a good system for drug delivery through the mammal membrane to targeted cells or tissues (Gujrati et al., 2016). Gujrat and co-workers, genetically engineered *S. cerevisiae* to produce vacuoles displaying human epidermal growth factor receptor 2 (HER2)-specific antibody. The vacuoles were charged with anticancer doxorubicin and then displayed to cancer cell culture. This system enhanced drug cellular entrance, which improved the drug delivery and avoided tumor growth (Gujrati et al., 2016). Studies in this area are increasing, pointing to *S. cerevisiae* as a potential candidate in nanoparticle delivery development.

4. Human premature aging

In addition to cancer and neurodegenerative disease, *S. cerevisiae* has been used to study human diseases related to aging and oxidative stress, as human premature aging. Progeroid syndromes are classified as monogenic syndrome because they are related to single mutations in genes from the DNA damage repair (mutations in RecQ helicases), Lamin A/C (LMNA) and Nucleotide Excise Repair (NER) (Martin and Oshima, 2000). There are more than ten different syndromes related to progeroid, differentiated mainly by the mutated protein, including Werner (WS) and Bloom's syndromes (BS) (mutations in WRN and BLM, helicases from the RecQ-like DNA helicases family) (Myung et al., 2001) and *Xeroderma pigmentosum* (XP) (mutation in XPG endonuclease) (Moriel-Carretero et al., 2015; Kang et al., 2014).

Some of the characteristics on progeroid syndromes, such as predisposition to cancer in BS and WS and the appearance of neuronal degeneration in XP, as well as the premature aging, are directly linked to genomic instability and defects in the protective mechanisms against oxidative stress (Herrero et al., 2008; Moriel-Carretero et al., 2015). ROS can induce DNA damage as double/single strand break, interstrand cross-link, and genomic instability observed in premature aging phenotypes (Hasty, 2003).

RecQ-like helicases are important, as the nucleotide excision repair (NER) system, to maintain genome integrity, sense DNA damage, and guarantee fork maintains the right replication process

(Yoshimura et al., 2017). Beside this, DNA damage caused by exposition to UV are initially repaired by the NER system (Kang et al., 2014).

To better understand the importance of WRN, BLM and XPG to protect human cells and how mutations can lead to progeroid syndromes, it is fundamental to work with an experimental cell model, which lacks WRN, BLM, and XPG and mimics the disease phenotype. The difficulty to obtain mutant animal cell lines (Aggarwal and Brosh Jr., 2010) and the high degree of conservation of RecQ-like DNA helicases (Mirzaei et al., 2011) are the main reasons why *S. cerevisiae* has become an useful model to study the molecular mechanisms involved in progeroid syndromes (Chen and Brill, 2014).

Sgs1 is the only RecQ-helicase in yeast homologue to human WRN and BLM (Madia et al., 2008). *S. cerevisiae* cells lacking *SGS1* have a short lifespan (Madia et al., 2008). Sgs1 and WRN interact with RPA (single-stranded DNA binding protein) as well as with Top3 (Schmidt et al., 2006; Levens et al., 2016).

The first yeast model to study progeroid syndrome was construct by expressing WRN and BLM in mutant cells *sgs1*. With this model, Aggarwal and Brosh showed that WRN is not able to rescue *sgs1* sensitivity to DNA damage, while BLM rescue the phenotype. This was the first time that an experiment showed that WRN and BLM are human RecQ-helicase with distinct functions (Aggarwal and Brosh, 2009). Beyond the function, using the same mutant, Chen and Brill determinate that the activity of WRN is associated to N-terminus and this helicase has a coiled coil domain (Chen and Brill, 2014). Using a double yeast mutant *sgs1top3*, Aggarwal & Brosh observed for the first time that WRN interact genetically with Top3, because WRN was able to restore phenotype in the double mutant (Aggarwal and Brosh, 2009). Working with combination of different mutation in genes related to DNA damage in mutant yeast cells *sgs1*, followed by expression of WRN, Madia and co-workers showed that WRN suppressed certain phenotypes, which indicates that the human RecQ helicase has some functional similarity to Sgs1(Madia et al., 2008).

To verify the relation between oxidative stress and progeroid syndrome, Madia and co-workers using *S. cerevisiae sgs1* cells showed that these cells treated with hydrogen peroxide had the lower chronological survival than the same mutant, without any kind of oxidative induction. The same was observed with cells treated with menadione. This result confirms that cells that lack Sgs1, in a model that mimics progeroid syndrome, have a rate of cell death higher that in control cell and are more sensitive to oxidative agents, confirmed that RecQ-helicases are essential to protect cells against oxidative stress (Madia et al., 2008).

S. cerevisiae is also useful to study XPG endonuclease, which are related to XS. As in WS and BS, *S. cerevisiae* has a homologue to XPG known as Rad2. The characterization and the role of XPG was only determined after the discovered of Rad2 (Kang et al., 2014). Patients with XS are extremely sensitive to UV; hence, they have high incidence of cancer (mainly skin cancer) (Moriel-Carretero et al., 2015). This was confirmed using yeast cells lacking RAD3 and treated with UV light, finding that these cells are more sensitive than a cell with no mutation. As UV light releases ROS, this also indicated that Rad and XPG are important to protect cells against oxidative stress (Herrera-Moyano et al., 2014).

Although *S. cerevisiae* has shown to be a very useful model to study progeroid syndromes, the literature still lacks works using yeast to better understand these syndromes. However, it is believed that in about ten years more researches will use yeast cell to gain new insight about cancer and aging related disease (Brosh and Bohr, 2007), to development treatment to cure or prevent this disease.

5. Conclusions

Some works have focused on the mechanism by which *S. cerevisiae* acquires tolerance to oxidative stress, which has been linked to diseases, such as cancer, and to the aging process. Because of the universal response to this stress, further insight into the response of *S. cerevisiae* will improve our understanding of human defense mechanisms and, consequently, the necessary foundation for practical applications. Remarkable examples of the utility of this organism for the elucidation of the molecular mechanisms involved in human diseases are the application of fundamental knowledge of cell cycle regulation and autophagy uncovered in yeast towards research in cancer and neurodegenerative diseases. These studies won the medicine Nobel prizes in 2002 and 2016, respectively. *S. cerevisiae* is a very attractive organism to work with, given its tractability, susceptibility to genetic modifications and the high genetic conservation with humans. For studies that aim to investigate the relation between oxidative stress and age-related diseases, the great advantage of *S. cerevisiae,* compared with other experimental models, is its capacity to grow using fermentative or oxidative metabolism. Thus, by shifting cells from the reduced environment of fermentation to a more oxidant condition, it is easy to verify the effect of oxidative stress on the molecular mechanisms of age-related diseases. Researchers have been humanizing yeast by expressing human proteins in yeast or even by humanizing entire pathways. The use of these 'humanized yeast systems' together with the metabolic versatility of this yeast should help identify disease-related cellular events and novel pharmacological agents to interfere with these processes.

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