Cell Cycle 13:21, 3336–3349; November 1, 2014; © 2014 Taylor & Francis Group, LLC

Quasi-programmed aging of budding yeast: a trade-off between programmed processes of cell proliferation, differentiation, stress response, survival and death defines yeast lifespan

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Keywords: cellular aging, cell growth and proliferation, cell survival, ecosystems, evolution, programmed cell death, longevity, yeast colony, yeast replicative and chronological aging, yeast

Abbreviations: D, diauxic growth phase; ERCs, extrachromosomal rDNA circles; IPOD, insoluble protein deposit; JUNQ, juxtanuclear quality control compartment; L, logarithmic growth phase; MBS, the mitochondrial back-signaling pathway; MTC, the mitochondrial translation control signaling pathway; NPCs, nuclear pore complexes; NQ, non-quiescent cells; PD, post-diauxic growth phase; Q, quiescent cells; Ras/cAMP/PKA, the Ras family GTPase/cAMP/protein kinase A signaling pathway; ROS, reactive oxygen species; RTG, the mitochondrial retrograde signaling pathway; ST, stationary growth phase; TOR/Sch9, the target of rapamycin/serine-threonine protein kinase Sch9 signaling pathway; UPR^{ER}, the unfolded protein response pathway in the endoplasmic reticulum; UPR^{mt}, the unfolded protein response pathway in mitochondria.

Recent findings suggest that evolutionarily distant organisms share the key features of the aging process and exhibit similar mechanisms of its modulation by certain genetic, dietary and pharmacological interventions. The scope of this review is to analyze mechanisms that in the yeast *Saccharomyces cerevisiae* underlie: (1) the replicative and chronological modes of aging; (2) the convergence of these 2 modes of aging into a single aging process; (3) a programmed differentiation of aging cell communities in liquid media and on solid surfaces; and (4) longevity-defining responses of cells to some chemical compounds released to an ecosystem by other organisms populating it. Based on such analysis, we conclude that all these mechanisms are programs for upholding the long-term survival of the entire yeast population inhabiting an ecological niche; however, none of these mechanisms is a "program of aging" - i.e., a program for progressing through consecutive steps of the aging process.

Introduction

Studies of the budding yeast *Saccharomyces cerevisiae*, a unicellular eukaryote amenable to comprehensive molecular analyses, have provided deep insights into mechanisms of cellular aging in multicellular eukaryotes.[1-5] These studies have been instrumental in identifying genes, uncovering signaling pathways and discovering chemical compounds shown to orchestrate a distinct set of cellular processes that define organismal longevity in eukaryotes across phyla.[5-21] These studies have revealed that the key features of the aging process and the mechanisms of its deceleration by certain longevity-extending genetic, dietary and pharmacological interventions are evolutionarily conserved.[1-3,6,8-10,15-19]

Two different methods have been established to investigate aging of budding yeast; each of them is designed to monitor a distinct aspect of the aging process. One of these 2 methods measures yeast replicative lifespan by assessing the number of asymmetric mitotic divisions a mother cell can undergo prior to cell cycle arrest.[2,3,5] Another method measures yeast chronological lifespan by assessing the length of time a cell remains viable following cell cycle arrest; a cell is considered to be viable if it can re-enter the cell cycle in response to addition of essential nutrients.[2-4,12,13] The use of these 2 methods has significantly advanced our understanding of cell-autonomous mechanisms that underlie the replicative and chronological paradigms of cellular aging in yeast.[2-5,12,13] However, these alternative methods have been employed to investigate the replicative and chronological modes of yeast aging separately from each other and under controllable laboratory conditions; such conditions may differ substantially from those existing within various natural ecosystems inhabited by budding yeast.[22-26] Moreover, recent studies have revealed several important features of yeast physiology and morphology, cell cycle regulation, quiescence-related differentiation, multicellular

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Submitted: 08/28/2014; Revised: 09/04/2014; Accepted: 09/09/2014
http://dx.doi.org/10.4161/15384101.2014.965063

organization, intercellular communications, ecology, and evolution; many of these features are likely to play key roles in defining longevity of budding yeast in Nature and/or under field-like laboratory conditions. First, studies in yeast cultured under controllable laboratory conditions have demonstrated that the rates of a stepwise progression of certain cellular processes through a series of "checkpoints" early in life of a yeast cell, prior to entry into a non-proliferative state, define its replicative and chronological lifespans; these processes include cell metabolism, growth and division, stress response, organelle dynamics, and macromolecular homeostasis (for a review, see refs. 3–5). Second, it has been shown that the replicative and chronological modes of yeast aging share some mechanisms and, thus, may converge into a single aging process; this process may progress through successive phases of quiescence and proliferation in response to certain environmental changes.[3,27-34] Third, it has been revealed that yeast cells cultured in glucose-based liquid media can exit the cell cycle from G_1 (or, under certain circumstances, from a cell cycle phase other than G_1) and enter a distinct differentiation program; this program yields a population of reproductively competent quiescent cells and several populations of non-quiescent cells that differ from each other in their ability to reproduce and/or survive.[35-43] Fourth, it has been demonstrated that yeast cells growing on solid surfaces are spatially organized into multicellular communities that exist as colonies or biofilms; individual cells within these communities grow, divide, communicate with each other, differentiate or commit programmed suicide in a manner which depends on their location within the community.[44-62] Fifth, it has been proposed that yeast cells within a natural ecosystem may respond to certain chemical compounds released to the ecosystem by other groups of prokaryotic and eukaryotic organisms; such response of yeast cells within the ecosystem may drive the evolution of yeast longevity regulation mechanisms.[63-67]

In this review we analyze these recent advances in our understanding of yeast aging within a logical framework of the so-called "quasi-programmed" concept of aging.[68-73] This concept: (1) considers aging not as a programmed (i.e., "active") process of functional decline or as a stochastic (i.e., "passive") process of molecular damage accumulation but as a late-life aftermath of the early-life programmed processes of cellular and organismal growth and reproduction; (2) posits that the rates with which these early-life programmed processes progress through late life define the rate of aging; and (3) postulates that the high rates of progression of these early-life programmed processes through late life cause so-called "hyperfunction" (or "hypertrophy"), thus accelerating the development of various age-related pathologies and ultimately causing aging-related death.[68-85] Based on presented here analysis of the recent advances in understanding of yeast aging, we propose that: (1) aging of budding yeast in the wild and/or under field-like laboratory conditions is a quasi-programmed process; and (2) the lifespan of yeast cells within an ecosystem is defined by a trade-off between programmed processes of cell proliferation, differentiation, stress response, survival and death.

Certain Early-Life Processes in a Mitotically Competent Mother Yeast Cell Define its Replicative Lifespan

Recent studies revealed that the rates and efficiencies of some cellular processes occurring early in life of a mother yeast cell, prior to loss of its ability to undergo asymmetric mitotic divisions, define the maximal number of daughter cells it can produce – i.e., define longevity of replicatively aging yeast.[3,5,20,21,78-80,85,86] These longevity-defining cellular processes within a replicatively aging mother cell: (1) are confined to various cellular compartments;[5,10,21,86,87] (2) take place during one of the 3 consecutive stages of replicative aging - which are called "early age", "intermediate age" and "late age", respectively;[5] (3) are coordinated and co-regulated in space and time (and some of them are inter-reliant on each other);[5,10,20,21,86,87] and (4) set up a rate of an age-related progressive accumulation of so-called "aging factors" (also known as "senescence factors") within the mother cell and, therefore, define its replicative lifespan.[3,5,20,21,86-91] These longevity-defining cellular processes within a replicatively aging mother cell include: (1) an increase in vacuolar pH during the early-age stage of replicative aging, which is followed by a gradual expansion of vacuoles during the intermediate-age stage and then by a dramatic enlargement of these organelles during the late-age stage;[5,21,86] (2) an appearance of protein aggregates due to a minor decline in proteostasis maintenance during the early-age stage of replicative aging, which is followed by a progressive accumulation of oxidatively damaged and aggregated proteins during the intermediate-age and late-age stages;[5,20,21,90] (3) a reduction in mitochondrial membrane potential, rise in the level of mitochondrial reactive oxygen species (ROS) and fragmentation of tubular mitochondria during the intermediate-age stage of replicative aging; such changes in mitochondria are followed by a massive aggregation of these organelles, further buildup of mitochondrial ROS and loss of mitochondrial DNA during the late-age stage;[5,86,92-95] (4) a rise in histone acetylation within subtelomeric chromatin regions of the nuclear DNA, the resulting release of histones from these regions and their transcriptional activation, and an accumulation of extrachromosomal rDNA circles (ERCs) in the nucleus during the intermediate-age stage of replicative aging; these changes are followed by a buildup of ERCs in the nucleus and loss of heterozygosity at the rDNA locus during the late-age stage;[5,21,90,96-98] and (5) an age-related gradual reduction in the efficiency of Pex5- and Pex7-driven protein import into the peroxisome, which causes a progressive development of a pro-aging metabolic pattern in peroxisomes and mitochondria (**Fig. 1**).[9,10,17]

The rates and efficiencies of all these longevity-defining cellular processes are modulated via 2 groups of cell-autonomous mechanisms operating within a mother yeast cell undergoing replicative aging.

One group of such mechanisms is aimed at reducing the rate of an age-related buildup of various aging factors within the mother cell; these mechanisms include: (1) mechanisms responsible for maintaining growth rate of the mother cell at a level which is (a) above a threshold level preventing a dilution of various

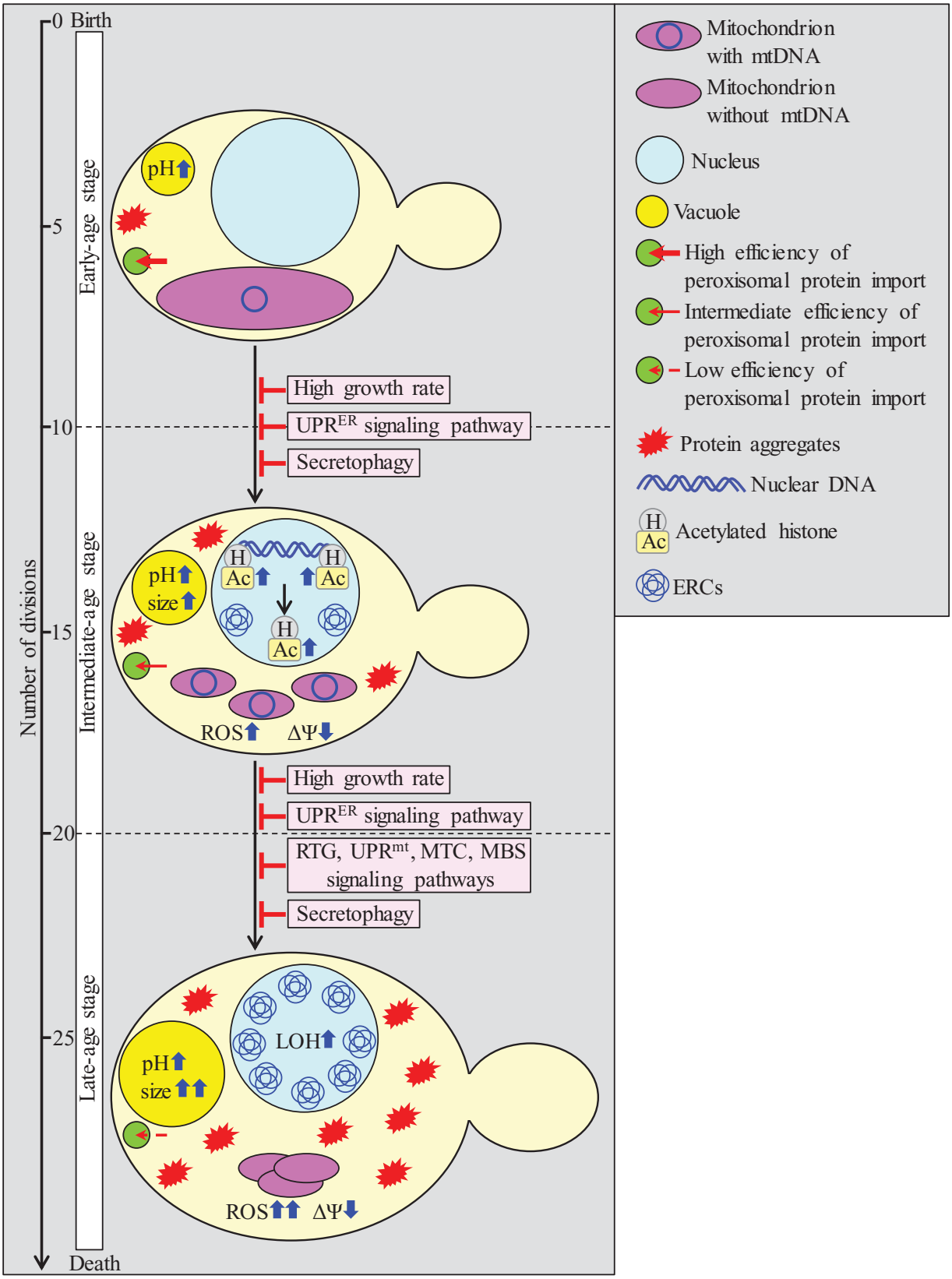

Figure 1. For figure legend, see page 3339.

aging factors within the mother cell via their transmission to the daughter cell but (b) below a threshold level allowing such transmitted aging factors to accumulate in the daughter cell in toxic quantities;[5,78,85] (2) the unfolded protein response signaling pathway in the endoplasmic reticulum (UPR^{ER}), which responds to an age-related accumulation of misfolded proteins in the ER by activating the expression of multiple genes implicated in stress resistance and cell wall integrity maintenance;[99] (3) the mitochondrial retrograde (RTG), unfolded protein response (UPR^{mt}), translation control (MTC) and back-signaling (MBS) pathways; these signaling pathways respond to an age-related decline in mitochondrial membrane potential, protein quality control, translation or ribosome assembly by stimulating transcription of many nuclear genes implicated in maintaining mitochondrial proteostasis, stabilizing nuclear and mitochondrial genomes, stress response, and various routes of central metabolism;[17,100-104] and (4) "secretophagy," a distinct form of age-related autophagy involved in the degradation of dysfunctional and aggregated organelles and proteins via a mechanism which is orchestrated by the Erg6 protein and executed by Atg15, a lipase whose re-location from the ER to vacuoles is mandatory for disintegrating membranes of autophagic bodies (**Fig. 1**).[105]

Another group of such mechanisms is aimed at increasing the efficiencies with which the mother cell retains various aging factors, thereby preventing their transmission into the daughter cell; these mechanisms include: (1) an Hsp104- and Sir2-dependent association of insoluble aggregated proteins with the actin cytoskeleton, a process which obstructs a free diffusion of such aggregates into the daughter cell (**Fig. 2A**);[5,20,21,106,107] (2) an Hsp104-driven sequestration of soluble misfolded proteins in nucleus-bound JUNQ (juxtanuclear quality control compartment), a process which concomitantly prevents a transmission of such misfolded proteins into the daughter cell and retains them within the mother cell for proteasomal degradation (**Fig. 2B**);[5,20,21,108,109] (3) an Hsp104- and Hsp42-dependent protective buildup of insoluble aggregated proteins in vacuole-bound IPOD (insoluble protein deposit); vacuoles containing IPOD are transmitted into the daughter cell less efficiently than vacuoles lacking it (**Fig. 2B**);[5,20,21,108-110] (4) a Sir2- and Myo2-driven movement of mitochondria from the mother cell to the daughter cell, a process in which fully functional mitochondria move on actin cables faster than dysfunctional ones (**Fig. 2C**);[21,92,111,112] (5) an association of ERCs formed in the mother cells with nuclear pore complexes (NPCs) whose lateral movement from the mother-cell side of the nuclear envelope to its daughter-cell side is prevented by a septin- and Bud6-dependent barrier existing at the bud neck; in this mechanism, NPCs are formed de novo in the daughter-cell side of the nuclear envelope (**Fig. 2D**);[21,113] (6) a distinct domain of the ER membrane assembled at the bud neck in a septin-, Bud1- and sphingolipid-dependent fashion; the formation of such domain in the mother-cell side of the cortical ER creates a barrier which prevents a lateral diffusion of misfolded (and, hence, toxic) transmembrane proteins into the daughter-cell side of the cortical ER (**Fig. 2E**);[114] and (7) an Inp2-dependent tagging of only fully functional peroxisomes within the mother cell for their segregation to the daughter cell; because Inp2 is a peroxisomal receptor for the class V myosin motor Myo2, such tagging contributes to the maintenance of age asymmetry between the mother and daughter cells by allowing only fully functional peroxisomes to be transferred to the daughter cell as Myo2 cargo moving on actin cables (**Fig. 2F**).[9,10,115,116]

It needs to be emphasized that the interplay between the aforementioned 2 groups of mechanisms operating within a mother yeast cell undergoing replicative aging defines several vital physiological traits. These traits play casual roles in yeast replicative aging; they include the rates and efficiencies with which the mother cell accumulates various aging factors, transmits these factors into the daughter cell, grows and undergoes asymmetric mitotic divisions, increases its size prior to bud formation, sporulates if deprived of nutrients, and responds to mild stresses and other environmental perturbations.[5,9,10,17,20,21,90,99-116] Thus, within a logical framework of the concept of quasi-programmed aging,[68-73] all of the mechanisms modulating the rates and efficiencies of accumulation and retention of various aging factors within the mother cell are programs for sustaining the long-term survival of the mother and daughter cells under various environmental conditions. However, none of these mechanisms is a "program of aging" - i.e., a program for a stepwise progression through consecutive steps of the aging process taking place in the mother or daughter cell.

Yeast Chronological Lifespan is Defined by Many Cellular Processes that Progress through a Series of Early-Life and Late-Life "Checkpoints"

We have recently reviewed in detail the cell-autonomous mechanisms underlying chronological aging of the yeast *S. cerevisiae*.[4] Briefly, longevity of chronologically aging yeast cultured under controllable laboratory conditions in liquid media is

Figure 1 (See previous page). Some processes in a mitotically competent mother yeast cell undergoing replicative aging define a rate with which it accumulates "aging factors." These longevity-defining cellular processes occur during one of the 3 consecutive stages of replicative aging called "early age," "intermediate age" and "late age." The rate of an age-related buildup of aging factors in the replicatively aging mother cell is modulated via several cell-autonomous mechanisms. Arrows next to the pro-aging cellular processes involved in the accumulation of aging factors in various cellular locations denote those of them that are stimulated or inhibited during a particular stage of replicative aging. Inhibition bars denote anti-aging cell-autonomous mechanisms that reduce the rates of the age-related buildup of certain aging factors in the replicatively aging mother cell. See text for additional details. ERCs, extrachromosomal rDNA circles; LOH, loss of heterozygosity at the rDNA locus; MBS, the mitochondrial back-signaling pathway; MTC, the mitochondrial translation control signaling pathway; mtDNA, mitochondrial DNA; ROS, reactive oxygen species; RTG, the mitochondrial retrograde signaling pathway; UPR^{ER}, the unfolded protein response signaling pathway in the endoplasmic reticulum; UPR^{mt}, the mitochondrial unfolded protein response signaling pathway; $\Delta\Psi$, electrochemical potential across the inner mitochondrial membrane.

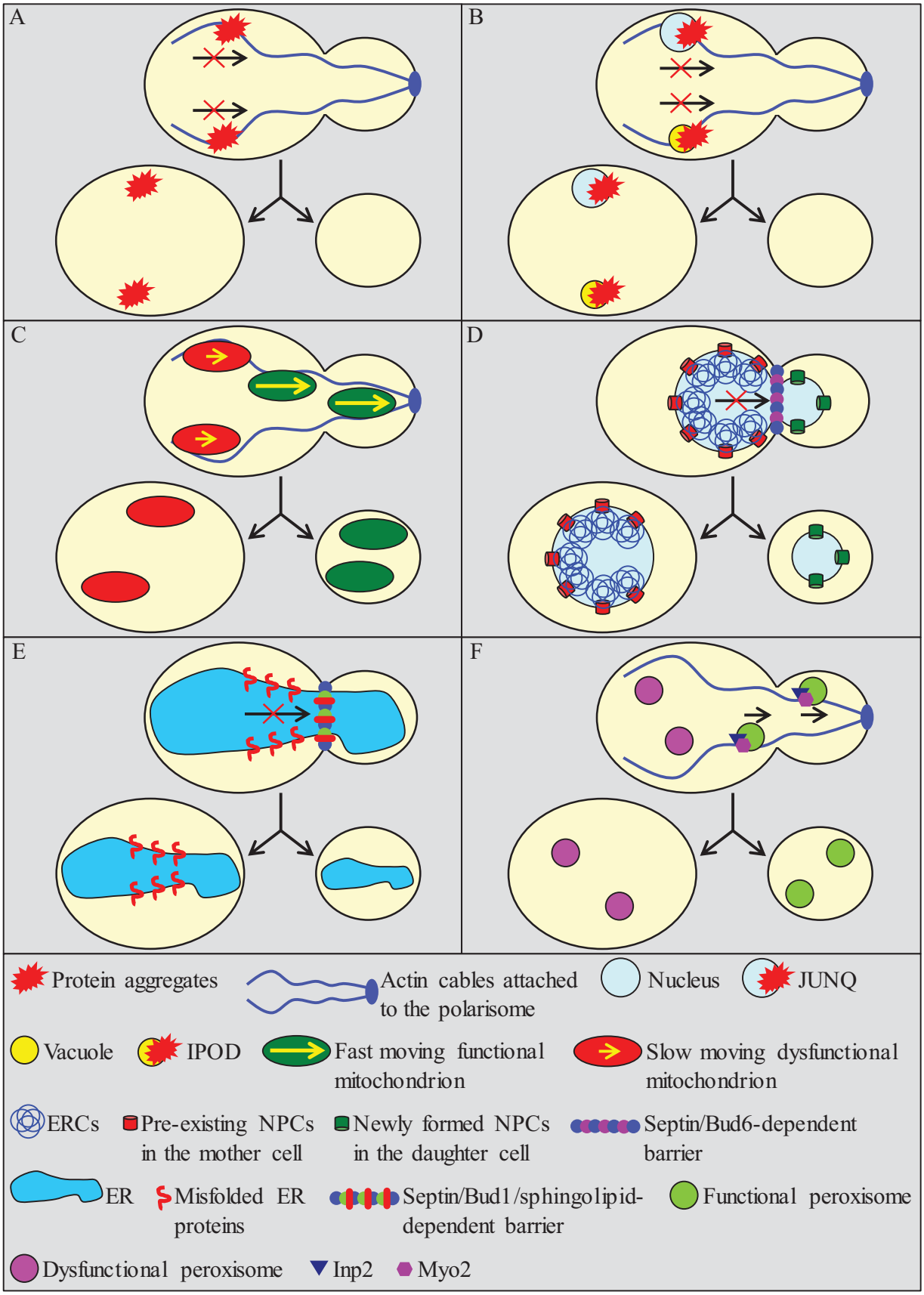

Figure 2. For figure legend, see page 3341.

defined by a distinct set of cellular processes that occur throughout lifespan, prior to an arrest of cell growth and division and following such arrest.[3,4,9,10,15,17,117-133] These processes include cell metabolism, growth, division, organelle biogenesis, interorganellar communication, macromolecular homeostasis, stress response and death.[2-4,17,119,126-131] We have proposed that all these longevity-defining cellular processes are integrated into a "biomolecular network".[4] Our concept of a biomolecular network underlying chronological aging in yeast posits that: (1) the network progresses through a series of lifespan checkpoints; the early-life checkpoints occur in logarithmic, diauxic and post-diauxic growth phases, whereas several late-life checkpoints occur in stationary growth phase; (2) at each of these checkpoints, several "master regulator" proteins monitor the intracellular concentrations of certain intermediates and/or products of particular metabolic pathways and assess the rates with which these key metabolites move within an elaborate network of interorganellar communications; (3) all these master regulator proteins have been shown to regulate longevity of chronologically aging yeast; (4) at each of the lifespan checkpoints, the checkpoint-specific master regulator proteins respond to age-related changes in the intracellular concentrations of the key metabolites and in the intensity of their interorganellar flow by amending the rates and efficiencies of cell metabolism, growth, division, organelle biogenesis, interorganellar communication, macromolecular homeostasis, stress response or death; and (5) by modulating such vital cellular processes throughout lifespan, these master regulator proteins act synergistically to orchestrate the development and maintenance of a pro- or anti-aging cellular pattern, thereby establishing the pace of cellular aging and defining yeast chronological lifespan (**Fig. 3**).[4]

It should be stressed that, as we recently discussed elsewhere,[4] our concept of a biomolecular network underlying chronological aging in yeast envisions that: (1) the inability of chronologically "young", proliferating cells to uphold the rates and efficiencies of the vital cellular processes integrated into the network above a critical threshold can elicit the excessive buildup of molecular and cellular damage in chronologically “old”, non-proliferating cells; and (2) the extreme cellular stress caused by such damage buildup in chronologically “old” cells can lead to their aging-related demise by stimulating apoptotic, regulated necrotic, autophagic and/or liponecrotic pathways known to be integrated into an age-associated network of programmed cell death.[3,4,6,18,134-137] Therefore, in terms of the concept of quasi-programmed aging,[68-73] the processes of metabolism, growth, division, organelle biogenesis, interorganellar communication, macromolecular homeostasis and stress response taking place within a chronologically aging yeast cell are programs for maintaining its long-term survival. Yet, none of these processes is a program for progressing through consecutive steps of the aging process and, hence, none of them is a “program of aging”.

The Replicative and Chronological Modes of Yeast Aging May Converge into a Single Aging Process

Traditionally, the replicative and chronological paradigms of yeast aging under controllable laboratory conditions are investigated independently of each other by monitoring the aging process in 2 different contexts.[3,119,138-141] However, several findings support the notion that these 2 paradigms share some mechanisms and, thus, are interconnected. Indeed, a caloric restriction (CR) diet is known to extend both the replicative and chronological lifespans of yeast.[1-3,33] Furthermore, genetic and pharmacological interventions attenuating signaling through the TOR/Sch9 (target of rapamycin/serine-threonine protein kinase Sch9) or Ras/cAMP/PKA (Ras family GTPase/cAMP/protein kinase A) pathway have been shown to exhibit longevity-extending effects in both paradigms of yeast aging;[1-3,29] these signaling pathways are known for their essential roles in modulating the rates and efficiencies of yeast cell metabolism, growth and division in response to changes in nutrient availability.[1-3] Moreover, chronological aging of yeast cells cultured under non-CR conditions in nutrient-rich or nutrient-limited liquid medium (or incubated at an elevated temperature in water) is known to coincide with their replicative aging; in fact, the longer a yeast cell is aged chronologically under such conditions the shorter its replicative lifespan becomes upon return to conditions that promote cell proliferation.[27,28,31,33] The extent of such chronological aging-associated reduction in yeast replicative lifespan can be lowered if: (1) yeast cells are aged chronologically under non-CR conditions that prevent a longevity-shortening phenomenon of medium acidification by these cells;[31] or (2) yeast cells are aged chronologically under longevity-extending CR conditions.[33] Thus, it is

Figure 2. (See previous page). Several cell-autonomous mechanisms modulate the efficiencies with which the mother cell retains various aging factors, thereby preventing their transmission into the daughter cell. (**A**) An association of insoluble protein aggregates with the actin cytoskeleton in the mother cell impedes a free diffusion of such aggregates into the daughter cell. (**B**) A sequestration of soluble misfolded proteins in nucleus-bound JUNQ (juxtanuclear quality control compartment) and a buildup of insoluble aggregated proteins in vacuole-bound IPOD (insoluble protein deposit) impede a transmission of such proteins into the daughter cell and retain them within the mother cell. (**C**) A movement of fully functional mitochondria on actin cables from the mother cell to the daughter cell is faster than that of dysfunctional mitochondria. (**D**) A septin- and Bud6-dependent barrier at the bud neck prevents a lateral movement of nuclear pore complexes (NPCs) from the mother-cell side of the nuclear envelope to its daughter-cell side; because extrachromosomal rDNA circles (ERCs) formed in the mother cells are attached to NPCs, these aging factors are retained by the mother cell. (**E**) A lateral diffusion of misfolded transmembrane proteins from the mother-cell side of the cortical endoplasmic reticulum (ER) into its daughter-cell side is prevented by a specialized domain of the cortical ER membrane; the formation of such ER membrane domain at the bud neck requires septin, Bud1 and sphingolipid. (**F**) Inp2 is a peroxisomal receptor for the class V myosin motor Myo2; the association of Inp2 only with fully functional peroxisomes within the mother cell allows the daughter cell to inherit only this kind of peroxisomes, which move with the help of Myo2 along tracks provided by actin cables. See text for additional details.

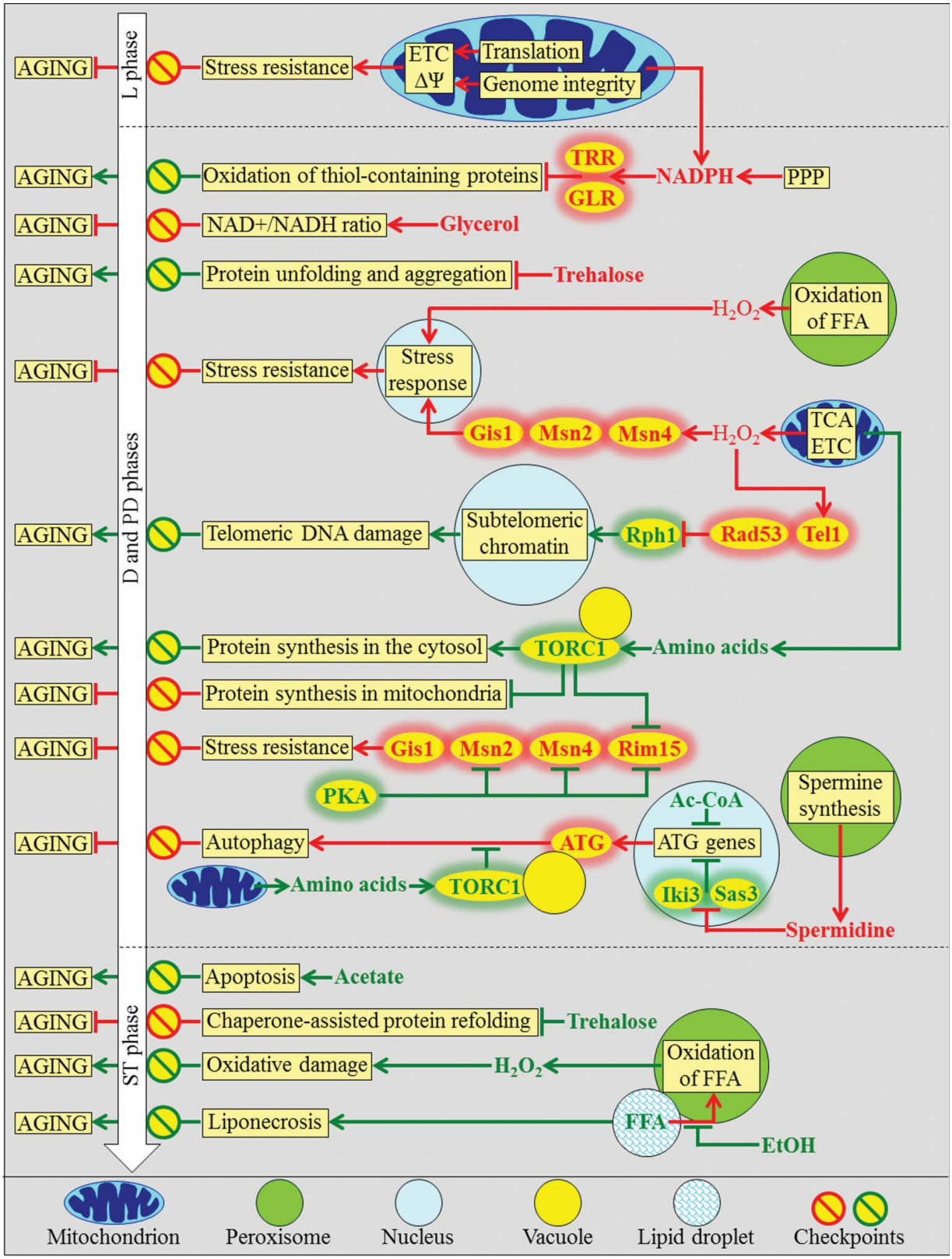

Figure 3. For figure legend, see page 3343.

conceivable that chronological aging of yeast cells cultured under non-CR conditions not only coincides with their replicative aging but may actually cause or accelerate such mode of aging. It seems that the efficiency with which yeast mitochondria maintain the electrochemical potential across their inner membrane is one of the essential cellular processes linking the replicative and chronological modes of aging; indeed, the lower mitochondrial membrane potential is in a yeast cell cultured under non-CR conditions the longer replicative lifespan such cell exhibits if it is returned to growth-promoting conditions.[33]

Noteworthy, the replicative and chronological modes of yeast aging do not overlap completely. Indeed, if they are investigated separately from each other in robust assays conducted under controllable laboratory conditions, it appears that: (1) only a limited number of single-gene-deletion mutations known to extend the replicative lifespan of yeast cells also extend their chronological lifespan;[1-3,29] and (2) buffering of various liquid media to different values of alkaline pH to prevent medium acidification extends yeast chronological lifespan but has no effect on yeast replicative lifespan.[31,142,143]

It needs to be emphasized that all of the assays for investigating the replicative and chronological paradigms of yeast aging - the ones conducted independently of each other and the ones conducted in combination with each other - were carried out under laboratory conditions that may differ markedly from those existing within various natural ecological niches inhabited by budding yeast.[22-26] Such natural habitats of different *S. cerevisiae* strains include the bark of oak trees, rotting tissues of cacti, plant flowers and fruits, desert soil, the midgut of insects, and infected immunocompromised patients.[25,26] Many "domesticated" strains of budding yeast also inhabit places associated with such important human activities as baking, brewing, winemaking and fermented beverage production.[22,25,26] We hypothesize that yeast strains facing diverse environmental constraints within such broad range of ecological niches may have evolved different kinds of the relationship between the replicative and chronological modes of yeast aging; each kind of such relationship is likely to be an adaptation evolved to sustain the long-term survival of the entire yeast population inhabiting a particular ecological niche. One kind of such relationship may involve a transition from the chronological mode to the replicative mode in a population of yeast cells that return from a quiescent state to a proliferative state in response to an increase in nutrient availability within their ecological niche; such transition may rejuvenate the population of yeast cells within the niche by preventing a transmission of aging factors accumulated within mother cells into newly formed daughter cells.[30-32]

The proposed here hypothesis also posits that the replicative and chronological modes of yeast aging may converge into a single aging process which is specific to the yeast population within a particular ecological niche. Furthermore, our hypothesis envisions that the postulated single aging process is a byproduct of an intricate network of cellular processes and intercellular communications defining the rates and efficiencies with which individual cells: (1) grow and divide; (2) differentiate into quiescent and non-quiescent cells; (3) switch mating-type by changing the allele at the *MAT* locus; (4) mate and then sporulate; (5) survive when nutrients are exhausted; (6) germinate from spores when nutrients become abundant again; (7) grow and survive within natural, clinical or industrial niches that are enriched or depleted in sugars, ethanol, acetate, glycerol or chemical compounds that are mildly toxic at high concentrations; and (8) commit themselves to apoptotic, regulated necrotic, autophagic and/or liponecrotic subroutines of programmed suicide if they are weakened or impaired, unable to reproduce sexually or asexually, inadequately adapted to natural variations in some environmental conditions, and/or release excessive amounts of ROS or other detrimental metabolites. It is conceivable that such intricate network is an evolutionary adaptation for sustaining the long-term survival of the entire yeast population inhabiting a particular ecological niche. Thus, in terms of the concept of quasi-programmed aging,[68-73] all cellular processes and intercellular communications integrated into the network are programmed to uphold such survival. However, none of these processes and communications is programmed to progress through consecutive steps of the aging process taking place in individual yeast cells within their population inhabiting a particular natural, clinical or industrial niche.

Programmed Differentiation of Yeast Cells Cultured in Liquid Media Yields Several Cell Populations that Differ in Their Longevities

When yeast cells cultured in a nutrient-rich liquid medium initially containing glucose consume this carbon source, they: (1) undergo a transition from L phase to D phase; (2) arrest in the G_1 phase of the cell cycle; and (3) enter a differentiation program which yields a population of quiescent (Q) cells existing in a

Figure 3. (See previous page). Some cellular processes in chronologically aging yeast are integrated into a biomolecular network. A stepwise progression of the network through a series of lifespan checkpoints existing in logarithmic (L), diauxic (D), post-diauxic (PD) and stationary (ST) growth phases is monitored by master regulator proteins. At each of the lifespan checkpoints, certain checkpoint-specific master regulator proteins respond to age-related changes in the intracellular concentrations of some key metabolites by modulating the rates and efficiencies of the longevity-defining cellular processes integrated into the network. Such action of master regulator proteins establishes the pace of cellular aging and defines yeast chronological lifespan. Activation arrows and inhibition bars signify pro-aging processes (shown in green color) or anti-aging processes (shown in red color). Pro-aging or anti-aging master regulator proteins are presented in green color or red color, respectively. Pro-aging or anti-aging metabolites are displayed in green color or red color, respectively. Ac-CoA, acetyl-CoA; ATG, components of the protein machinery involved in autophagy; ETC, electron transport chain; EtOH, ethanol; FFA, non-esterified ("free") fatty acids; GLR, glutathione reductase; PPP, the pentose phosphate pathway; PKA, protein kinase A; TCA, tricarboxylic acid cycle; TORC1, target of rapamycin complex 1; TRR, thioredoxin reductase; $\Delta\Psi$, electrochemical potential across the inner mitochondrial membrane.

specialized nonproliferative state called G_0 as well as several populations of non-quiescent (NQ) cells.[35,36,38,41-43] The population of Q cells committed to this cell fate upon transition from L phase to D phase consists mainly of daughters, and also includes "young" mothers that underwent a single budding event.[35,36,38,41] Q cells exhibit a distinct set of morphological, biochemical and physiological features. These cells: (1) are unbudded, uniform in size and surrounded by a thickened cell wall; (2) are denser than NQ cells; (3) amass such reserve carbohydrates as trehalose and glycogen; (4) are highly refractive by phase-contrast microscopy; (5) are viable - i.e., they exhibit high metabolic activity monitored using a fluorescent reporter molecule; (6) display low levels of intracellular ROS; (7) contain fully functional mitochondria exhibiting high respiratory efficiency; (8) can synchronously reenter the cell cycle if returned to growth-promoting conditions; (9) are reproductively competent - i.e., they can form colonies when plated on a fresh solid medium; (10) are resistant to chronic oxidative, thermal and osmotic stresses; and (11) are genomically stable.[35,38,41,42] The population of NQ cells committed to this cell fate upon transition from L phase to D phase is comprised of "old" mothers that underwent several budding events.[35,36,38,41] NQ cell population is heterogeneous; in ST phase it consists of 3 cell types, including: (1) viable and reproductively competent cells exhibiting genomic instability, high levels of ROS and dysfunctional mitochondria that are unable to respire; (2) viable but reproductively incompetent cells, which may derive from the reproductively competent NQ cells; and (3) cells that display characteristic traits of apoptotic and/or necrotic programmed death subroutines; these cells may originate from the reproductively incompetent NQ cells.[35,36,38,41] Noteworthy, it has been proposed that late in ST phase the sub-population of reproductively competent NQ cells may undergo a gradual replenishment due to an aging-related differentiation of Q cells.[38,41]

It needs to be emphasized that both the commitment of yeast to the differentiation into Q cells and several populations of NQ cells, as well as the maintenance of such commitment, are programmed processes; indeed, they both are orchestrated by: (1) Xbp1, a transcription repressor of numerous genes implicated in cell growth and division; (2) the TOR/Sch9 and Ras/cAMP/PKA signaling pathways known for their essential roles in modulating the rates and efficiencies of cell metabolism, growth and division in response to changes in nutrient availability; (3) Snf1, an AMP-activated serine/threonine protein kinase essential for maintaining energy homeostasis during D phase; and (4) Pho85, a cyclin-dependent kinase orchestrating various metabolic processes upon cell entry into the Q state.[36,40,43,144,145] Furthermore, it is also important to note that yeast cell populations can respond to a depletion of nutrients other than glucose (such as nitrogen or phosphate) by entering discrete differentiation programs and accessing distinct Q states;[146] it is tempting to speculate that cells existing in such distinct Q states differ in their long-term viabilities following cell cycle arrest in the G_1 phase and, thus, vary in their longevities. Moreover, in should be stressed that yeast cell population can enter the Q state in cell cycle phases other than G_1;[39] yeast cells that enter the Q state after being arrested in the S or G_2 phase of the cell cycle are known to exhibit shortened replicative lifespans.[147]

Altogether, these findings support the notion that a programmed differentiation of yeast cultured under controllable laboratory conditions in liquid media yields several cell types that differ in their longevities. Furthermore, the number of such differentiated cell types and their longevities may vary within a significantly broader range in yeast populations that inhabit diverse natural, clinical or industrial niches within various ecosystems. Thus, the differentiation of yeast communities into Q cells and several populations of NQ cells is a program for adapting to wide-range variations in nutrients availability within the ecological niche inhabited by a particular yeast community; different types of yeast cells formed during such programmed differentiation vary in their longevities. However, within a logical framework of the concept of quasi-programmed aging,[68-73] such differentiation is not a program for progressing through consecutive steps of the aging process and, thus, is not a "program of aging".

Cell-Non-Autonomous Mechanisms Define Longevity of Differentiated Yeast Cells Attached to Solid Surfaces and Organized into Multicellular Communities

It is well known that yeast cells attached to solid surfaces develop multicellular communities in the wild and under laboratory conditions; these communities of numerous differentiated cells with specialized functions are organized into colonies or biofilms.[44,46,51,53,54,57,61] Individual yeast cells within these communities undergo global metabolic reprogramming; such reprogramming progresses through 2 reversible phases of ammonia release and 2 phases of medium acidification, impacts various metabolic pathways, and orchestrates a multistep process of horizontal and vertical differentiation of the entire community.[45-48,50-53,57,59-61] Furthermore, yeast cells within these multicellular communities are involved in quorum sensing by communicating with each other via a unidirectional or bidirectional flow of certain chemical compounds.[45-47,50-54,57,59-61] Moreover, yeast cells within these multicellular communities exhibit differential patterns of global gene expression, which depends on cell position within the community and may cause the development of a pro- or anti-aging cellular pattern within a particular region of such community.[47,48,52,53,56-58,60-62] Noteworthy, yeast cells within these multicellular communities grow, divide, differentiate, communicate with each other or commit programmed suicide in a manner which depends on their location within the community and is driven by quorum sensing.[45-54,57,59-61] It needs to be emphasized that these multicellular yeast communities differentiate into several subpopulations of nondividing chronologically aging cells that exhibit wide-range variations with respect to their central metabolism patterns, amino acid and nucleotide metabolism rates, storage carbohydrates and neutral lipids quantities, mitochondrial functionalities and ROS levels, noncoding RNA quantities, protein synthesis rates, autophagic and proteasomal protein

degradation efficiencies, growth and division rates, stress adaptabilities and susceptibilities, and survival capabilities.[46-62]

All of the above cell-non-autonomous mechanisms operating within a horizontally and vertically organized community of differentiated yeast cells define dissimilar longevities of the cells positioned within different regions of such community.[46,47,51-55,57,61] Hence, the differentiation of individual yeast cells and their sub-populations within various parts of such community is a program for maintaining the long-term survival of the whole community, even though some individual cells and their sub-populations unintentionally make altruistic sacrifices to execute this program.[46,47,51-55,57,61] Yet, in terms of the concept of quasi-programmed aging,[68-73] such differentiation is not a program for progressing through consecutive steps of the aging process and, thus, is not a "program of aging".

Interspecies Communications within an Ecosystem May Drive the Evolution of Yeast Longevity Regulation Mechanisms

It has been demonstrated that bacteria, plants and animals synthesize and release into the environment certain chemical compounds that under controllable laboratory conditions can extend longevity of evolutionarily distant organisms.[1,2,6,7,63-67] Indeed, soil bacteria are known to synthesize the lipophilic macrocyclic lactone called rapamycin;[148] this fungicide not only impedes proliferation of fungal competitors within a natural ecosystem but also extends longevity of yeast, worms, fruit flies and mice by inhibiting the nutrient-sensory protein kinase TOR (Tor1 in yeast).[1,2,66-68,149] Furthermore, plants and other autotrophic organisms have been shown to respond to various environmental stresses by synthesising and releasing into natural ecosystems certain secondary metabolites called xenohormetic phytochemicals;[63-65] they include polyphenols (such as resveratrol, butein and fisetin), curcumin, caffeine and spermidine - all known for their abilities to increase longevity of yeast and various other organisms by targeting different cellular processes and signaling pathways.[6,63-65] Moreover, mammals are known to synthesize and release into natural ecosystems bile acids;[150] these molecules have been shown to extend yeast chronological lifespan by altering mitochondrial membrane lipidome and triggering major changes in mitochondrial morphology and function.[7,125,128,130]

Based on our analysis of how all these natural chemical compounds released into the environment by some organisms composing an ecosystem extend longevity of other organisms within this ecosystem, we recently proposed a hypothesis of the xenohormetic, hormetic and cytostatic selective forces that may drive the evolution of yeast longevity regulation mechanisms at the ecosystemic level.[66,67] Our hypothesis posits that yeast cells inhabiting a natural ecosystem may specifically respond to some chemical compounds released to such ecosystem by other organisms; such response of yeast cells within the ecosystem may: (1) elicit a cytostatic or hormetic effect in these cells; (2) trigger the development of a pro- or anti-aging physiological pattern within these cells; and (3) drive the evolution of yeast longevity regulation mechanisms toward the maintenance of a finite lifespan of these cells.[66,67] Our hypothesis envisions that such response of yeast cells to the chemical compounds released to the ecosystem by other organisms is a program for increasing the chances of yeast cells to survive various environmental alterations by undergoing specific changes in yeast physiology; some of these changes play essential roles in regulating yeast longevity.[66,67] However, within a logical framework of the concept of quasi-programmed aging,[68-73] such response of yeast cells to the chemical compounds released to the ecosystem by other organisms is not a "program of aging" - i.e., a program for progressing through consecutive steps of the aging process.

Conclusions

In this review we analyzed mechanisms underlying the replicative and chronological modes of yeast aging, their convergence into a single aging process within natural ecological niches, programmed differentiation of aging yeast communities cultured in liquid media or attached to solid surfaces, and a longevity-defining response of yeast cells to certain chemical compounds released to an ecosystem by other organisms inhabiting this ecosystem. Our analysis implies that all these mechanisms are intricate programs for sustaining the long-term survival of the entire yeast population inhabiting a particular natural, industrial, clinical or laboratory niche; to execute such programs, some individual cells altruistically (but involuntarily) sacrifice their own lives. However, none of these mechanisms is a program for progressing through consecutive steps of the aging process. We therefore concluded that aging of budding yeast in natural, industrial, clinical and laboratory niches is a late-life aftermath of the early-life programmed processes of cell growth, division, differentiation and stress response; a term "quasi-programmed" has been coined for such mode of aging in higher eukaryotic organisms.[68-73] We also concluded that the lifespan of a yeast cell within an ecosystem is defined by a trade-off between programmed processes of cell growth, reproduction, differentiation, stress response, survival and death.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We are grateful to current and former members of the Titorenko laboratory for discussions.

Funding

This research was supported by grants from the NSERC of Canada and Concordia University Chair Fund to VIT. AP was supported by a Frederick Banting and Charles Best Canada Master's Scholarship Award from the Canadian Institutes of Health Research. V.S. was supported by an Undergraduate Summer Award from the NSERC of Canada. VIT is a Concordia University Research Chair in Genomics, Cell Biology and Aging.

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