HHS Public Access

Author manuscript

Curr Genet. Author manuscript; available in PMC 2019 May 21.

Published in final edited form as:

Curr Genet. 2018 August ; 64(4): 761–767. doi:10.1007/s00294-017-0799-z.

Emerging Roles for Sphingolipids in Cellular Aging

Pushpendra Singh[1,2,*] and **Rong Li**[3,4]

[1]Laboratory of Adjuvant and Antigen Research, US Military HIV Research Program, Walter Reed Army Institute of Research, 503 Robert Grant Avenue, Silver Spring, MD 20910, USA.

[2]U.S. Military HIV Research Program, Henry M. Jackson Foundation for the Advancement of Military Medicine, 6720A Rockledge Drive, Bethesda, MD 20817, USA.

[3]Center for Cell Dynamics, Department of Cell Biology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA.

[4]Department of Chemical and Biomolecular Engineering, Whiting School of Engineering, Johns Hopkins University, Baltimore, Maryland 21218, USA.

Abstract

Aging is a gradual loss of physiological functions as organisms' progress in age. Although aging in multicellular organisms is complex, some fundamental mechanisms and pathways may be shared from the single cellular yeast to human. Budding yeast *Saccharomyces cerevisiae* has been established model system for aging studies. A yeast cell divides asymmetrically to produce two cells that differ in size and age. The one that is smaller coming from bud is a newborn cell that with a full replicative potential head irrespective of the replicative age of its mother – the larger cell from which the bud grows out before division. The age asymmetry between daughter and mother is thought to be dependent on asymmetric segregation of certain factors such as protein aggregates, extrachromosomal DNA (ERCs) and dysfunctional organelles during successive cell divisions of the yeast replicative lifespan (RLS). It is also thought that certain plasma membrane proteins, in particular multidrug-resistant (MDR) proteins, asymmetrically partition between the mother and the bud based on the age of the polypeptides. Functional decline associated with the molecular aging of those proteins contributes to the fitness decline at advance age. In our recent study, we showed that sphingolipids facilitate the age-dependent segregation of MDRs between daughter and mother cell. In this review, we highlight and discuss the potential mechanisms by which sphingolipids regulate the aging process in yeast and cells of vertebrate animals including human.

Keywords

Sphingolipids; Replicative Aging; Multidrug Resistance Proteins; Asymmetric Cell Division

[*]Correspondence: psingh@hivresearch.org.

Conflict of Interest

Authors declare that they have no conflict of interest.

Introduction.

Demographics of the world are changing rapidly where old populations are growing at unprecedented rate. Aging is the leading risk factor for an array of diseases that negatively affect people's quality of life (Jin, Simpkins, Ji, Leis, & Stambler, 2014; Reeve, Simcox, & Turnbull, 2014). If the aging process can be intervened, it could reduce the incidences and impede the progression of age-related diseases and extend the health lifespan. Aging studies are therefore of great importance in biomedical research. Aging is a multifaceted process influenced by many intrinsic and extrinsic factors (Kirkwood, 2008). A mechanistic understanding of the aging process is required for developing effective therapeutic intervention of age-related diseases. Despite the differences in the manifestation of aging in diverse organism (Kirkwood, 2005; Shmookler Reis, 2012), some molecular processes may be conserved. Budding yeast *Saccharomyces cerevisiae* has been a valuable experimental system for gaining insights into the aging process on the cellular level (Kaeberlein, Burtner, & Kennedy, 2007). Lessons learnt in yeast are likely to be useful for the understanding of aging in vertebrates including human (Wasko & Kaeberlein, 2014). In this review, we will first discuss the possible mechanisms by which sphingolipids regulate the aging process in yeast and then discuss the relevance of sphingolipid-regulated processes for cellular aging in vertebrate animals including human.

Factors influencing aging during yeast RLS.

Budding yeast can go through two different types of lifespans: replicative and chronological. Replicative lifespan (RLS) is the number of daughters produced by each actively dividing mother cell before it dies, whereas chronological lifespan (CLS) is the length of time spent a non-dividing yeast cell stay viable in the stationary phase (G_0-arrested) (Polymenis & Kennedy, 2012). During RLS, yeast cells go through many morphological and physiological changes that result in the intrinsic age-related decline in reproductive potential, termed functional senescence, which does not apply to stationary phase cells during CLS (Jazwinski, 2002). Since biological aging process is the product of functional senescence, RLS appears to be a better model for cellular aging. Importantly, recent studies in animal models and mammalian stem-like cells suggest that replicative aging in yeast may be a model for stem cell aging (L. Liu & Rando, 2011; Schultz & Sinclair, 2016). Stem cells exhibit functional decline with age also termed as 'stem cell exhaustion', a hallmark of organismal aging (Lopez-Otin, Blasco, Partridge, Serrano, & Kroemer, 2013), as it leads to the decline in organisms' capacity for tissue repair and regeneration.

Under unperturbed conditions, each round of cell division in *S. cerevisiae* produces an older mother cell and a younger daughter cell. Factors that contribute to this age asymmetry are segregated between the mother and the bud prior to cytokinesis (Henderson & Gottschling, 2008). The asymmetry of aging in yeast has been attributed to progressive and asymmetric accumulation of detrimental factors (Henderson & Gottschling, 2008), such as extra chromosomal rDNA circles (ERCs) (Sinclair & Guarente, 1997) and oxidatively damaged proteins (Aguilaniu, Gustafsson, Rigoulet, & Nystrom, 2003; Erjavec, Larsson, Grantham, & Nyström, 2007), as well as the gradual decline of organelle activities, such as that of mitochondria (Delaney et al., 2013; McFaline-Figueroa et al., 2011) or vacuole (A. L.

Hughes & Gottschling, 2012) in the aging mother cell. Interestingly, retrotransposons have also been speculated to contribute to cellular aging by promoting the genomic instability or activating DNA damage checkpoints during the course of aging (Maxwell, 2016). In addition, certain plasma membrane proteins belonging to the MDR family of proteins are asymmetrically partitioned between the mother and the bud with respect to polypeptide age. MDRs are multi-pass transmembrane proteins that carry out nutrient uptake and removal of harmful metabolites from the cell (Ernst, Klemm, Schmitt, & Kuchler, 2005). It was observed that MDR protein synthesis is regulated in a cell-cycle dependent manner (Eldakak et al., 2010). After the original discovery, the list of these asymmetrically partitioned proteins was expanded using a systematic approach to identify genes encoding long-lived and asymmetrically retained proteins (LARPs) in the yeast genome (Thayer et al., 2014). MDRs are shown to associate stably with the cell cortex (Eldakak et al., 2010; Ganguly, Singh, Manoharlal, Prasad, & Chattopadhyay, 2009; P. Singh et al., 2017; Spira et al., 2012) and exhibit limited turnover with each cell cycle (Eldakak et al., 2010). Through computational modeling based on experimentally determined parameters, it was speculated that the ‘average age’ of MDR polypeptides increases in mother cell of advanced replicative age. Importantly, functional efficiency of MDRs decreases with progress in replicative age, likely due to both protein turnover and accumulation of damage. While loss of MDRs reduces RLS, increasing the copy number of certain MDR extend, suggesting that MDRs are beneficial factor during cellular aging and their progressive decline in function contributes to viability loss at advanced replicative age.

Mechanism behind stable retention of MDRs at cell cortex.

Through a combination of genetics and multi-color high-resolution live cell microscopy approaches, we showed that the newly synthesized MDRs are preferentially deposited into the bud PM prior to cytokinesis, whereas old MDR proteins are retained by the mother cell (P. Singh et al., 2017). Thus, mother cell maintains its own original set of MDRs while bud cell receives most of the newly synthesized set during the cell cycle in which it is born. In addition, MDRs are stably associated with cortex and do not exhibit lateral mobility in the PM (Eldakak et al., 2010; Ganguly et al., 2009; P. Singh et al., 2017; Spira et al., 2012). Thus, the segregation of MDRs based on polypeptide age is maintained through their cell cycle dependent synthesis, polarized deposition and restriction of lateral mobility in the yeast PM. We investigated several possibilities that could restrict MDR diffusion in the PM of dividing yeast.

First, we investigated the role of septin cytoskeleton assembly in restricting the mobility of MDRs at bud-neck. The septin assembly at bud neck is known to act as a diffusion barrier for known aging factors such as protein aggregates and ERCs in dividing yeast cell (Caudron & Barral, 2009; Gladfelter, Pringle, & Lew, 2001; Mostowy & Cossart, 2012; Ong, Wloka, Okada, Svitkina, & Bi, 2014; Saarikangas & Barral, 2016). Upon a thorough investigation, we concluded that septin/ER barrier is not responsible for the age-dependent MDR segregation in daughter and mother cells (Pushpendra Singh et al., 2017). Second, we examined whether eisosome structures in yeast plasma membrane (PM) could restrict the diffusion of MDRs to maintain their asymmetric distribution in dividing cell. Similar to MDRs, eisosomes are asymmetrically distributed immobile structures in yeast PM (Douglas

& Konopka, 2014). Interestingly, eisosomes act as a membrane reservoir and can regulate the exchange of lipids in PM (Kabeche, Howard, & Moseley, 2015). Therefore, the possibility that eisosomes regulate MDR asymmetry through modulating the membrane packing appeared attractive. Pil1, an essential subunit of eisosomes, is required for eisosome biogenesis in yeast (Moreira, Walther, Aguilar, & Walter, 2009). However, we observed no significant change in age-dependent bud-mother asymmetry and lateral diffusion of Tpo1, an example MDR protein, in *Δpil1* strain, suggesting that eisosomes do not play a role in this process (unpublished observation).

All MDRs are transmembrane proteins that contain multiple long (≥24 aminoacid residues) transmembrane domains. Interestingly, sphingolipids contain unusually long acyl chains in comparison to phospholipids in yeast (Ejsing et al., 2009). Lipid-protein interactions are known to play crucial function in restricting the lateral diffusion of membrane protein (Gambin et al., 2006; Lee, 2004). Further, long acyl chains of lipids are known to stabilize transmembrane proteins and peptides through providing hydrophobic match in the membrane bilayer (Ramadurai, Holt, et al., 2010; Ramadurai, Duurkens, Krasnikov, & Poolman, 2010). Indeed, we found that age-dependent MDR asymmetry between the mother and bud is compromised with a concomitant increase in their lateral diffusion in the PM under sphingolipid depletion (Pushpendra Singh et al., 2017). Importantly, shortening of the long acyl chain of sphingolipid to the chain length of phospholipids resulted in a significant loss of mother-bud asymmetry with a concomitant increase in Tpo1 mobility in the yeast PM (Pushpendra Singh et al., 2017). We proposed that the long acyl chains of sphingolipids provide hydrophobic match to the long transmembrane domains of MDR proteins. This way, thermodynamically unfavorable interactions between nonpolar hydrophobic transmembrane aminoacids of MDRs with polar aqueous environment are minimized. At the molecular level, long chains of sphingolipids could directly interact with long transmembrane domain of proteins increasing the local thickness of the membrane to provide hydrophobic match to long transmembrane domains. Or, they might form patches of thicker membrane domains surrounding MDR proteins. All these possibilities may co-exist and remain to be further investigated. At the biochemical and biophysical level, lipid chain length modulates the binding affinities of lipids with long transmembrane proteins through hydrophobic match. The chain length dependences of the lipid association with long transmembrane of proteins is the result of minimization of the overall thermodynamic energy due to net impact of elastic chain extension and reduction in the contact of hydrophobic patches transmembrane with polar surfaces of the membrane (Marsh, 2008). Importantly, sphingolipids are known to interact with sterols to form stable membrane domains sometimes called lipid rafts in live cells (Simons & Ikonen, 1997). However, we did not observe any impact of alteration in ergosterol synthesis on the lateral diffusion and asymmetry of MDR proteins between the mother and daughter cell in dividing yeast (Pushpendra Singh et al., 2017). These results suggest that sphingolipid-mediated diffusion barrier is distinct and operates through a different mechanism from that of the classic lipid rafts.

Do sphingolipids create membrane diffusion barrier in other organisms?

Sphingolipids constitute a significant fraction of the PM and contain acyl chains of C16–24, often saturated in most mammalian cells. However, epidermal keratinocytes and male germ

cells largely express sphingolipids with long chains (C26–C36) during their differentiation and maturation (Sandhoff, 2010). Long chain sphingolipids in keratinocytes participate in the covalent binding of –OH ceramides to corneocyte proteins (predominantly involucrin) and the formation of a water-resistant structure in the stratum corneum, also designated as cornified lipid envelope (CLE) thus are crucial for maintaining proper skin barrier function (Radner et al., 2010), and speculated to be involved in differentiation of spermatocytes/spermatids (Poulos, Johnson, Beckman, White, & Easton, 1987). At the molecular level, long chain sphingolipids harbor unique biophysical properties not possessed by regular chain sphingolipids such as effects on membrane packing, microdomain formation, and signaling across the membrane (Kasahara & Sanai, 2000; Simons & Ikonen, 1997; Sonnino et al., 2009). For example, studies using artificial lipid bilayers have suggested that the long chain fatty acyl chains in sphingolipids may interdigitate with the opposing leaflet and facilitate lipid micro-domain formation (Morrow, Singh, Lu, & Grant, 1995).

Yeast sphingolipids consist exclusively of saturated long chain (C26) sphingolipids (Ejsing et al., 2009). Synthesis of long chain sphingolipids is important for yeast, and mutant strains with a low amount of long chain sphingolipids exhibit defects in vesicular transport (Obara, Kojima, & Kihara, 2013). Long chain sphingolipids may have a conserved role in vesicular trafficking systems across the phyla (Sassa & Kihara, 2014). In our study, we observed that MDR asymmetry in budding yeast is maintained through the restriction of their lateral mobility. To understand if these functions of sphingolipids in maintaining MDR asymmetric distribution is conserved in the distantly related fission yeast (Sipiczki, 2000), we studied the distribution and lateral mobility of Mrh1, the Tpo1 homolog in fission yeast. As opposed to budding yeast but similar to mammalian cells, fission yeast divides symmetrically (Balasubramanian, Bi, & Glotzer, 2004). A cylindrical fission yeast cell divide in the middle through formation of a septum to produce two daughter cells of identical size. A daughter cell grows linearly first at the old end (monopolar growth) and later at both ends (bipolar growth) (Mitchison & Nurse, 1985). It is unclear if fission yeast also contains long acyl chain sphingolipids. Importantly, sphingolipids are important membrane constituent, they regulate several cellular processes such as cell proliferation, endocytosis and trafficking (Hannun & Obeid, 2008). Interestingly, terminal sphingolipid in fission yeast is mannosylinositol phosphorylceramide (MIPC) as opposed to mannosyldiinositol phosphorylceramide (M(IP)2C) in budding yeast (Nakase et al., 2010). Similar to the pattern in budding yeast, the growing ends of fission yeast, equivalent to the growing bud, do not carry Mrh1 whereas the protein decorates the non-growing mid part of the cell cortex (Pushpendra Singh et al., 2017). Importantly, sphingolipid depletion resulted in a loss of this Mrh1 pattern in fission yeast with an increase in the lateral diffusion of Mrh1 (Pushpendra Singh et al., 2017). Thus, sphingolipid mediated membrane diffusion barrier exists in two evolutionary distant yeast that differ in their cell division pattern. It will be interesting to investigate in future work whether sphingolipids also help determine the distribution of PM proteins in metazoan organisms by restricting their lateral diffusion.

Sphingolipids in aging.

Lipid alterations are developmentally regulated and occur with age in different tissues, organs in human and other organisms (J. R. Hughes et al., 2012). It is generally accepted that

lipid turnover is rapid and dysregulation in turnover results in disease (Dawidowicz, 1987; J. Liu, Zeng, et al., 2013; Phillips, Ursell, Wiggins, & Sens, 2009). Lipid turnover rate varies widely depending on cell, tissue and organ in humans. For example, mean lipid age in human adipocytes is 1.6 years whereas age of adipocyte is 9.5 years suggesting that lipids, on average, are replaced 6 times in the lifespan of an adipocyte in human (Arner et al., 2011). In the lens, pronounced alterations has been reported in lipid composition over the lifespan of human (J. R. Hughes et al., 2012)., but sphingolipids do not turn over and are long-lived in the center of the human ocular lens during the entire human lifespan (Jessica R. Hughes et al., 2015). Direct links between sphingolipids and the pathogenesis of ocular diseases have been discussed elsewhere (Chen, Chan, Stone, & Mandal, 2014). Sphingolipids are involved in a number of cellular processes such as cell proliferation, endocytosis and trafficking (Hannun & Obeid, 2008). Importantly, sphingolipids have been implicated in cellular aging across different phyla (An, Na, Bielawski, Hannun, & Kasper, 2011; Cutler, Thompson, Camandola, Mack, & Mattson, 2014; J. R. Hughes et al., 2012). There appear to be more than one sphingolipid-mediated mechanism in cellular aging. Sphingolipids have been found to accumulate in long-living cohort of human population and were declared as markers and biological modulators of healthy aging in humans by providing a better antioxidant capacity and participating in membrane remodeling process (Collino et al., 2013; Montoliu et al., 2014). A *Drosophila* mutant that exhibits ~70% decrease in sphingolipid level, shows decreased membrane packing and enhanced oxidative damage to cellular proteins possibly due to increased susceptibility to reactive oxygen species (ROS). This in turn results in shorter lifespan of *Drosophila* (Rao et al., 2007). Furthermore, a significant drop in glucosylceramide sphingolipid was observed in aged $CD4^+$ T cells, and a reduction in glucosylceramide level using pharmacological inhibitors resulted in age-related impairments in $CD4^+$ T cell function (Molano et al., 2012). These data implied beneficial functions of sphingolipids during aging, consistent with our finding that that alteration in sphingolipid level and structure leads to reduction in yeast RLS which is largely due to the loss of MDR from mother cell with replicate age (Pushpendra Singh et al., 2017). However, it was reported that downregulation of sphingolipids using pharmacological and genetic approaches through inhibition of serine palmitoyl transferase (SPT) activity, the first enzyme in sphingolipid biosynthesis, extends chronological life span (CLS) in budding yeast (Huang, Liu, & Dickson, 2012; J. Liu, Huang, et al., 2013). However, CLS in yeast may be quite different from physiological aging process studied elsewhere because yeast cells evaluated for CLS are in a low metabolic state, which is different from highly active dividing cells or differentiated non-dividing cells with specialized functions.

Effect of sphingolipids on other asymmetric aging factors.

As discussed above, sphingolipids appear to be a critical player in cellular aging. However, their mechanism of action are not clearly understood. For instance, while they were found to regulate the asymmetric segregation of MDRs during yeast RLS, their role in the asymmetric distribution of other known aging determinants has not been studied systematically. Clay et al. reported that misfolded proteins in the ER are confined into the mother compartment of budding yeast cells through a sphingolipid-mediated diffusion barrier in the ER-membrane at the bud neck (Clay et al., 2014). Sphingolipids are

synthesized at ER but are not known to be present in ER membrane, consistent with the observation of fast diffusion of Tpo1 in ER membrane in our study (Pushpendra Singh et al., 2017). Thus, it is unclear how sphingolipids restrict the diffusion of misfolded proteins in the ER. In another example, sphingolipids are shown to be involved in the mitochondrial segregation in dividing yeast as increased level of sphingolipid bases altered the mitochondria protein level (Yi et al., 2016). In addition, an increase in sphingolipids inhibited mitochondrial fusion and resulted in their fragmentation leading to their functional dysregulation. These results suggest that abnormally increased sphingolipid could accelerate the aging process by impairing mitochondrial structural integrity and functions (Yi et al., 2016).

Conclusion and Perspective.

Increasing evidence suggests that sphingolipids are involved in cellular aging from unicellular yeast to human. However, their role appears to be quite complex as this lipid participates in a myriad of cellular processes. While recent data showed that sphingolipids help maintain the age-dependent MDR protein asymmetry between the mother and daughter in dividing yeast cells, the underlying molecular and biophysical mechanisms remain to be further studied. Do long chains of sphingolipids directly interact with MDR or create lateral domains of thicker membrane in the PM? Do other lipids cooperate with sphingolipids in these mechanisms? Furthermore, to what extent the hydrophobic matching between long chain sphingolipid and long transmembrane sequences of MDRs helps restrict latter's diffusion in the PM. As sphingolipid depletion did not completely release the restriction of MDRs diffusion, what other mechanisms independent of sphingolipids might be at work? Additionally, it would be interesting to examine if similar to MDR synthesis, sphingolipid synthesis is regulated in a cell cycle dependent manner and shows any spatial pattern. The rate of sphingolipid turnover in yeast will also be of interest as this may further validate this lipid's role as an aging determinant. To this end, a biosensor for sphingolipids would be required to track their synthesis and distribution in spatiotemporal manner. Such tools, as well as insights from simple model organisms such as yeast, will help further illuminate the role of sphingolipids lipids in cellular aging

Acknowledgment

This work was supported by the grant R35 GM118172 from the National Institutes of Health to R. Li. The authors apologize to the researchers whose work could not be cited or not cited fully due to space limitation.

References

Aguilaniu H, Gustafsson L, Rigoulet M, & Nystrom T (2003). Asymmetric inheritance of oxidatively damaged proteins during cytokinesis. Science, 299(5613), 1751–3. 10.1126/science.1080418 [PubMed: 12610228]

An D, Na C, Bielawski J, Hannun YA, & Kasper DL (2011). Membrane sphingolipids as essential molecular signals for Bacteroides survival in the intestine. Proceedings of the National Academy of Sciences, 108(Supplement 1), 4666–4671. 10.1073/pnas.1001501107

Arner P, Bernard S, Salehpour M, Possnert G, Liebl J, Steier P, … Spalding KL (2011). Dynamics of human adipose lipid turnover in health and metabolic disease. Nature, 478(7367), nature10426. 10.1038/nature10426

Balasubramanian MK, Bi E, & Glotzer M (2004). Comparative analysis of cytokinesis in budding yeast, fission yeast and animal cells. Curr Biol, 14(18), R806–18. 10.1016/j.cub.2004.09.022 [PubMed: 15380095]

Caudron F, & Barral Y (2009). Septins and the lateral compartmentalization of eukaryotic membranes. Dev Cell, 16(4), 493–506. 10.1016/j.devcel.2009.04.003 [PubMed: 19386259]

Chen H, Chan AY, Stone DU, & Mandal NA (2014). Beyond the Cherry-Red Spot: Ocular Manifestations of Sphingolipid-mediated Neurodegenerative and Inflammatory Disorders. Survey of Ophthalmology, 59(1). 10.1016/j.survophthal.2013.02.005

Clay L, Caudron F, Denoth-Lippuner A, Boettcher B, Buvelot Frei S, Snapp EL, & Barral Y (2014). A sphingolipid-dependent diffusion barrier confines ER stress to the yeast mother cell. Elife, 3, e01883 10.7554/eLife.01883 [PubMed: 24843009]

Collino S, Montoliu I, Martin F-PJ, Scherer M, Mari D, Salvioli S, … Rezzi S (2013). Metabolic signatures of extreme longevity in northern Italian centenarians reveal a complex remodeling of lipids, amino acids, and gut microbiota metabolism. PloS One, 8(3), e56564 10.1371/journal.pone.0056564 [PubMed: 23483888]

Cutler RG, Thompson KW, Camandola S, Mack KT, & Mattson MP (2014). Sphingolipid metabolism regulates development and lifespan in Caenorhabditis elegans. Mechanisms of Ageing and Development, 0, 9–18. 10.1016/j.mad.2014.11.002

Dawidowicz EA (1987). Dynamics of membrane lipid metabolism and turnover. Annual Review of Biochemistry, 56, 43–61. 10.1146/annurev.bi.56.070187.000355

Delaney JR, Ahmed U, Chou A, Sim S, Carr D, Murakami CJ, … Kaeberlein M (2013). Stress profiling of longevity mutants identifies Afg3 as a mitochondrial determinant of cytoplasmic mRNA translation and aging. Aging Cell, 12(1), 156–166. 10.1111/acel.12032 [PubMed: 23167605]

Douglas LM, & Konopka JB (2014). Fungal membrane organization: the eisosome concept. Annual Review of Microbiology, 68, 377–393. 10.1146/annurev-micro-091313-103507

Ejsing CS, Sampaio JL, Surendranath V, Duchoslav E, Ekroos K, Klemm RW, … Shevchenko A (2009). Global analysis of the yeast lipidome by quantitative shotgun mass spectrometry. Proc Natl Acad Sci U S A, 106(7), 2136–41. 10.1073/pnas.0811700106 [PubMed: 19174513]

Eldakak A, Rancati G, Rubinstein B, Paul P, Conaway V, & Li R (2010). Asymmetrically inherited multidrug resistance transporters are recessive determinants in cellular replicative ageing. Nat Cell Biol, 12(8), 799–805. 10.1038/ncb2085 [PubMed: 20657593]

Erjavec N, Larsson L, Grantham J, & Nyström T (2007). Accelerated aging and failure to segregate damaged proteins in Sir2 mutants can be suppressed by overproducing the protein aggregation-remodeling factor Hsp104p. Genes & Development, 21(19), 2410–2421. 10.1101/gad.439307 [PubMed: 17908928]

Ernst R, Klemm R, Schmitt L, & Kuchler K (2005). Yeast ATP-Binding Cassette Transporters: Cellular Cleaning Pumps In B.-M. in Enzymology (Ed.) (Vol. 400, pp. 460–484). Academic Press 10.1016/S0076-6879(05)00026-1

Gambin Y, Lopez-Esparza R, Reffay M, Sierecki E, Gov NS, Genest M, … Urbach W (2006). Lateral mobility of proteins in liquid membranes revisited. Proceedings of the National Academy of Sciences of the United States of America, 103(7), 2098–2102. 10.1073/pnas.0511026103 [PubMed: 16461891]

Ganguly S, Singh P, Manoharlal R, Prasad R, & Chattopadhyay A (2009). Differential dynamics of membrane proteins in yeast. Biochem Biophys Res Commun, 387(4), 661–5. 10.1016/j.bbrc.2009.07.054 [PubMed: 19615977]

Gladfelter AS, Pringle JR, & Lew DJ (2001). The septin cortex at the yeast mother-bud neck. Curr Opin Microbiol, 4(6), 681–9. [PubMed: 11731320]

Hannun YA, & Obeid LM (2008). Principles of bioactive lipid signalling: lessons from sphingolipids. Nature Reviews. Molecular Cell Biology, 9(2), 139–150. 10.1038/nrm2329 [PubMed: 18216770]

Henderson KA, & Gottschling DE (2008). A mother's sacrifice: what is she keeping for herself? Curr Opin Cell Biol, 20(6), 723–8. 10.1016/j.ceb.2008.09.004 [PubMed: 18848886]

Huang X, Liu J, & Dickson RC (2012). Down-regulating sphingolipid synthesis increases yeast lifespan. PLoS Genetics, 8(2), e1002493 10.1371/journal.pgen.1002493 [PubMed: 22319457]

Hughes AL, & Gottschling DE (2012). An early age increase in vacuolar pH limits mitochondrial function and lifespan in yeast. Nature, 492(7428), 261–5. 10.1038/nature11654 [PubMed: 23172144]

Hughes JR, Deeley JM, Blanksby SJ, Leisch F, Ellis SR, Truscott RJ, & Mitchell TW (2012). Instability of the cellular lipidome with age. Age (Dordr), 34(4), 935–47. 10.1007/s11357-011-9293-6 [PubMed: 21894448]

Hughes JR, Levchenko VA, Blanksby SJ, Mitchell TW, Williams A, & Truscott RJW (2015). No turnover in lens lipids for the entire human lifespan. ELife, 4 10.7554/eLife.06003

Jazwinski SM (2002). Growing old: metabolic control and yeast aging. Annu Rev Microbiol, 56, 769–92. 10.1146/annurev.micro.56.012302.160830 [PubMed: 12213938]

Jin K, Simpkins JW, Ji X, Leis M, & Stambler I (2014). The Critical Need to Promote Research of Aging and Aging-related Diseases to Improve Health and Longevity of the Elderly Population. Aging and Disease, 6(1), 1–5. 10.14336/AD.2014.1210 [PubMed: 25657847]

Kabeche R, Howard L, & Moseley JB (2015). Eisosomes provide membrane reservoirs for rapid expansion of the yeast plasma membrane. J Cell Sci, 128(22), 4057–62. 10.1242/jcs.176867 [PubMed: 26403204]

Kaeberlein M, Burtner CR, & Kennedy BK (2007). Recent developments in yeast aging. PLoS Genetics, 3(5), e84 10.1371/journal.pgen.0030084 [PubMed: 17530929]

Kasahara K, & Sanai Y (2000). Functional roles of glycosphingolipids in signal transduction via lipid rafts. Glycoconjugate Journal, 17(3–4), 153–162. [PubMed: 11201786]

Kirkwood TB (2005). Understanding the odd science of aging. Cell, 120(4), 437–47. 10.1016/j.cell.2005.01.027 [PubMed: 15734677]

Kirkwood TB (2008). Understanding ageing from an evolutionary perspective. J Intern Med, 263(2), 117–27. 10.1111/j.1365-2796.2007.01901.x [PubMed: 18226090]

Lee AG (2004). How lipids affect the activities of integral membrane proteins. Biochim Biophys Acta, 1666(1–2), 62–87. 10.1016/j.bbamem.2004.05.012 [PubMed: 15519309]

Liu J, Huang X, Withers BR, Blalock E, Liu K, & Dickson RC (2013). Reducing sphingolipid synthesis orchestrates global changes to extend yeast lifespan. Aging Cell, 12(5), 833–841. 10.1111/acel.12107 [PubMed: 23725375]

Liu J, Zeng F-F, Liu Z-M, Zhang C-X, Ling W, & Chen Y-M (2013). Effects of blood triglycerides on cardiovascular and all-cause mortality: a systematic review and meta-analysis of 61 prospective studies. Lipids in Health and Disease, 12, 159 10.1186/1476-511X-12-159 [PubMed: 24164719]

Liu L, & Rando TA (2011). Manifestations and mechanisms of stem cell aging. The Journal of Cell Biology, 193(2), 257–266. 10.1083/jcb.201010131 [PubMed: 21502357]

Lopez-Otin C, Blasco MA, Partridge L, Serrano M, & Kroemer G (2013). The hallmarks of aging. Cell, 153(6), 1194–217. 10.1016/j.cell.2013.05.039 [PubMed: 23746838]

Marsh D (2008). Energetics of Hydrophobic Matching in Lipid-Protein Interactions. Biophysical Journal, 94(10), 3996–4013. 10.1529/biophysj.107.121475 [PubMed: 18234817]

Maxwell PH (2016). What might retrotransposons teach us about aging? Current Genetics, 62(2), 277–282. 10.1007/s00294-015-0538-2 [PubMed: 26581630]

McFaline-Figueroa JR, Vevea J, Swayne TC, Zhou C, Liu C, Leung G, … Pon LA. (2011). Mitochondrial quality control during inheritance is associated with lifespan and mother-daughter age asymmetry in budding yeast. Aging Cell, 10(5), 885–895. 10.1111/j.1474-9726.2011.00731.x [PubMed: 21726403]

Mitchison JM, & Nurse P (1985). Growth in cell length in the fission yeast Schizosaccharomyces pombe. Journal of Cell Science, 75, 357–376. [PubMed: 4044680]

Molano A, Huang Z, Marko MG, Azzi A, Wu D, Wang E, … Meydani SN (2012). Age-dependent changes in the sphingolipid composition of mouse CD4+ T cell membranes and immune synapses implicate glucosylceramides in age-related T cell dysfunction. PloS One, 7(10), e47650 10.1371/journal.pone.0047650 [PubMed: 23110086]

Montoliu I, Scherer M, Beguelin F, DaSilva L, Mari D, Salvioli S, … Collino S (2014). Serum profiling of healthy aging identifies phospho- and sphingolipid species as markers of human longevity. Aging, 6(1), 9–25. 10.18632/aging.100630 [PubMed: 24457528]

Moreira KE, Walther TC, Aguilar PS, & Walter P (2009). Pil1 controls eisosome biogenesis. Mol Biol Cell, 20(3), 809–18. 10.1091/mbc.E08-03-0313 [PubMed: 19037108]

Morrow MR, Singh D, Lu D, & Grant CW (1995). Glycosphingolipid fatty acid arrangement in phospholipid bilayers: cholesterol effects. Biophysical Journal, 68(1), 179–186. 10.1016/S0006-3495(95)80173-6 [PubMed: 7711240]

Mostowy S, & Cossart P (2012). Septins: the fourth component of the cytoskeleton. Nat Rev Mol Cell Biol, 13(3), 183–94. 10.1038/nrm3284 [PubMed: 22314400]

Nakase M, Tani M, Morita T, Kitamoto HK, Kashiwazaki J, Nakamura T, … Takegawa K (2010). Mannosylinositol phosphorylceramide is a major sphingolipid component and is required for proper localization of plasma-membrane proteins in Schizosaccharomyces pombe. Journal of Cell Science, 123(Pt 9), 1578–1587. 10.1242/jcs.059139 [PubMed: 20388730]

Obara K, Kojima R, & Kihara A (2013). Effects on vesicular transport pathways at the late endosome in cells with limited very long-chain fatty acids. Journal of Lipid Research, 54(3), 831–842. 10.1194/jlr.M034678 [PubMed: 23325927]

Ong K, Wloka C, Okada S, Svitkina T, & Bi E (2014). Architecture and dynamic remodelling of the septin cytoskeleton during the cell cycle. Nature Communications, 5, ncomms6698. 10.1038/ncomms6698

Phillips R, Ursell T, Wiggins P, & Sens P (2009). Emerging roles for lipids in shaping membrane-protein function. Nature, 459(7245), 379–85. 10.1038/nature08147 [PubMed: 19458714]

Polymenis M, & Kennedy BK (2012). Chronological and replicative lifespan in yeast. Cell Cycle, 11(19), 3531 10.4161/cc.22041 [PubMed: 22951539]

Poulos A, Johnson DW, Beckman K, White IG, & Easton C (1987). Occurrence of unusual molecular species of sphingomyelin containing 28–34-carbon polyenoic fatty acids in ram spermatozoa. The Biochemical Journal, 248(3), 961–964. [PubMed: 3435495]

Radner FPW, Streith IE, Schoiswohl G, Schweiger M, Kumari M, Eichmann TO, … Haemmerle G (2010). Growth retardation, impaired triacylglycerol catabolism, hepatic steatosis, and lethal skin barrier defect in mice lacking comparative gene identification-58 (CGI-58). The Journal of Biological Chemistry, 285(10), 7300–7311. 10.1074/jbc.M109.081877 [PubMed: 20023287]

Ramadurai S, Duurkens R, Krasnikov VV, & Poolman B (2010). Lateral diffusion of membrane proteins: consequences of hydrophobic mismatch and lipid composition. Biophysical Journal, 99(5), 1482–1489. 10.1016/j.bpj.2010.06.036 [PubMed: 20816060]

Ramadurai S, Holt A, Schäfer LV, Krasnikov VV, Rijkers DTS, Marrink SJ, … Poolman B (2010). Influence of hydrophobic mismatch and amino acid composition on the lateral diffusion of transmembrane peptides. Biophysical Journal, 99(5), 1447–1454. 10.1016/j.bpj.2010.05.042 [PubMed: 20816056]

Rao RP, Yuan C, Allegood JC, Rawat SS, Edwards MB, Wang X, … Acharya JK (2007). Ceramide transfer protein function is essential for normal oxidative stress response and lifespan. Proceedings of the National Academy of Sciences of the United States of America, 104(27), 11364–11369. 10.1073/pnas.0705049104 [PubMed: 17592126]

Reeve A, Simcox E, & Turnbull D (2014). Ageing and Parkinson's disease: Why is advancing age the biggest risk factor? Ageing Research Reviews, 14(100), 19–30. 10.1016/j.arr.2014.01.004 [PubMed: 24503004]

Saarikangas J, & Barral Y (2016). Protein aggregation as a mechanism of adaptive cellular responses. Current Genetics, 62(4), 711–724. 10.1007/s00294-016-0596-0 [PubMed: 27032776]

Sandhoff R (2010). Very long chain sphingolipids: tissue expression, function and synthesis. FEBS Letters, 584(9), 1907–1913. 10.1016/j.febslet.2009.12.032 [PubMed: 20035755]

Sassa T, & Kihara A (2014). Metabolism of Very Long-Chain Fatty Acids: Genes and Pathophysiology. Biomolecules & Therapeutics, 22(2), 83–92. 10.4062/biomolther.2014.017 [PubMed: 24753812]

Schultz MB, & Sinclair DA (2016). When stem cells grow old: phenotypes and mechanisms of stem cell aging. Development (Cambridge, England), 143(1), 3–14. 10.1242/dev.130633

Shmookler Reis RJ (2012). Coming to terms with complexity: limits to a reductionist view of aging. Frontiers in Genetics, 3, 149 10.3389/fgene.2012.00149 [PubMed: 22969788]

Simons K, & Ikonen E (1997). Functional rafts in cell membranes. Nature, 387(6633), 569–72. 10.1038/42408 [PubMed: 9177342]

Sinclair DA, & Guarente L (1997). Extrachromosomal rDNA circles--a cause of aging in yeast. Cell, 91(7), 1033–42. [PubMed: 9428525]

Singh P, Ramachandran SK, Zhu J, Kim BC, Biswas D, Ha T, … Li R (2017). Sphingolipids Facilitate Age Asymmetry of Membrane Proteins in Dividing Yeast Cells. Mol Biol Cell. 10.1091/mbc.E17-05-0335

Singh P, Ramachandran SK, Zhu J, Kim BC, Biswas D, Ha T, … Li R (2017). Sphingolipids Facilitate Age Asymmetry of Membrane Proteins in Dividing Yeast Cells. Molecular Biology of the Cell. 10.1091/mbc.E17-05-0335

Sipiczki M (2000). Where does fission yeast sit on the tree of life? Genome Biology, 1(2), REVIEWS1011. 10.1186/gb-2000-1-2-reviews1011

Sonnino S, Prinetti A, Nakayama H, Yangida M, Ogawa H, & Iwabuchi K (2009). Role of very long fatty acid-containing glycosphingolipids in membrane organization and cell signaling: the model of lactosylceramide in neutrophils. Glycoconjugate Journal, 26(6), 615–621. 10.1007/s10719-008-9215-8 [PubMed: 19015977]

Spira F, Mueller NS, Beck G, von Olshausen P, Beig J, & Wedlich-Soldner R (2012). Patchwork organization of the yeast plasma membrane into numerous coexisting domains. Nat Cell Biol, 14(6), 640–8. 10.1038/ncb2487 [PubMed: 22544065]

Thayer NH, Leverich CK, Fitzgibbon MP, Nelson ZW, Henderson KA, Gafken PR, … Gottschling DE (2014). Identification of long-lived proteins retained in cells undergoing repeated asymmetric divisions. Proc Natl Acad Sci U S A, 111(39), 14019–26. 10.1073/pnas.1416079111 [PubMed: 25228775]

Wasko BM, & Kaeberlein M (2014). Yeast replicative aging: a paradigm for defining conserved longevity interventions. FEMS Yeast Res, 14(1), 148–59. 10.1111/1567-1364.12104 [PubMed: 24119093]

Yi JK, Xu R, Jeong E, Mileva I, Truman J-P, Lin C-L, … Mao C (2016). Aging-related elevation of sphingoid bases shortens yeast chronological life span by compromising mitochondrial function. Oncotarget, 7(16), 21124–21144. 10.18632/oncotarget.8195 [PubMed: 27008706]