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A system wide view of replicative aging in budding yeast

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Document Version

Publisher's PDF, also known as Version of record

Publication date:
2016

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Citation for published version (APA):

Janssens, G. E. (2016). A system wide view of replicative aging in budding yeast: Protein biogenesis machinery as a driver of the aging process; molecular and cellular properties associated to longevity in single cells; and the relevance of aging in yeast to aging in humans. [Groningen]: University of Groningen.

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Bibliography

- [1] L. Fontana, L. Partridge, V.D. Longo, Extending healthy life span--from yeast to humans., *Science*. 328 (2010) 321–326. doi:10.1126/science.1172539.
- [2] T.B.L. Kirkwood, Understanding ageing from an evolutionary perspective, in: *J. Intern. Med.*, 2008: pp. 117–127. doi:10.1111/j.1365-2796.2007.01901.x.
- [3] L. Hayflick, Biological aging is no longer an unsolved problem, in: *Ann. N. Y. Acad. Sci.*, 2007: pp. 1–13. doi:10.1196/annals.1395.001.
- [4] S.I.S. Rattan, Theories of biological aging: genes, proteins, and free radicals., *Free Radic. Res.* 40 (2006) 1230–1238. doi:10.1080/10715760600911303.
- [5] J.P. De Magalhães, Programmatic features of aging originating in development: Aging mechanisms beyond molecular damage?, *FASEB J.* 26 (2012) 4821–4826. doi:10.1096/fj.12-210872.
- [6] A.M. Kligman, P. Zheng, R.M. Lavker, The anatomy and pathogenesis of wrinkles., *Br. J. Dermatol.* 113 (1985) 37–42. doi:10.1111/j.1365-2133.1985.tb02042.x.
- [7] J.L. Contet-Audonneau, C. Jeanmaire, G. Pauly, A histological study of human wrinkle structures: Comparison between sun-exposed areas of the face, with or without wrinkles, and sun-protected areas, *Br. J. Dermatol.* 140 (1999) 1038–1047. doi:10.1046/j.1365-2133.1999.02901.x.
- [8] R. Arking, The biology of aging: observations and principles, 2006. doi:10.1080/03601270701498491.
- [9] R. Buffa, G.U. Floris, P.F. Putzu, E. Marini, Body composition variations in ageing., *Coll. Antropol.* 35 (2011) 259–265.
- [10] T. Niccoli, L. Partridge, Ageing as a risk factor for disease, *Curr. Biol.* 22 (2012). doi:10.1016/j.cub.2012.07.024.
- [11] M. Stanton, The High Concentration of U.S. Health Care Expenditures, *Res. Action*, Rockville, MD Agency Healthc. Res. Qual. (2006).
- [12] R. Lee, The Demographic Transition: Three Centuries of Fundamental Change, *J. Econ. Perspect.* 17 (2003) 167–190. doi:10.1257/089533003772034943.
- [13] L.E. Hebert, P.A. Scherr, L.A. Beckett, M.S. Albert, D.M. Pilgrim, M.J. Chown, et al., Age-specific incidence of Alzheimer's disease in a community population., *JAMA*. 273 (1995) 1354–1359. doi:10.1001/jama.1995.03520410048025.

Bibliography

- [14] J.P. de Magalhães, How ageing processes influence cancer., *Nat. Rev. Cancer.* 13 (2013) 357–65. doi:10.1038/nrc3497.
- [15] T. Craig, C. Smelick, R. Tacutu, D. Wuttke, S.H. Wood, H. Stanley, et al., The Digital Ageing Atlas: integrating the diversity of age-related changes into a unified resource, *Nucleic Acids Res.* 43 (2014) D873–D878. doi:10.1093/nar/gku843.
- [16] M.-G. Hong, A.J. Myers, P.K.E. Magnusson, J.A. Prince, Transcriptome-wide assessment of human brain and lymphocyte senescence., *PLoS One.* 3 (2008) e3024. doi:10.1371/journal.pone.0003024.
- [17] G.E.J. Rodwell, R. Sonu, J.M. Zahn, J. Lund, J. Wilhelmy, L. Wang, et al., A transcriptional profile of aging in the human kidney, *PLoS Biol.* 2 (2004). doi:10.1371/journal.pbio.0020427.
- [18] J.M. Zahn, R. Sonu, H. Vogel, E. Crane, K. Mazan-Mamczarz, R. Rabkin, et al., Transcriptional profiling of aging in human muscle reveals a common aging signature, *PLoS Genet.* 2 (2006) 1058–1069. doi:10.1371/journal.pgen.0020115.
- [19] J.P. de Magalhães, J. Curado, G.M. Church, Meta-analysis of age-related gene expression profiles identifies common signatures of aging, *Bioinformatics.* 25 (2009) 875–881. doi:10.1093/bioinformatics/btp073.
- [20] T. Lu, Y. Pan, S.-Y. Kao, C. Li, I. Kohane, J. Chan, et al., Gene regulation and DNA damage in the ageing human brain., *Nature.* 429 (2004) 883–891. doi:10.1038/nature02661.
- [21] C. Colantuoni, B.K. Lipska, T. Ye, T.M. Hyde, R. Tao, J.T. Leek, et al., Temporal dynamics and genetic control of transcription in the human prefrontal cortex, *Nature.* 478 (2011) 519–523. doi:10.1038/nature10524.
- [22] O.R. Jones, A. Scheuerlein, R. Salguero-Gómez, C.G. Camarda, R. Schaible, B.B. Casper, et al., Diversity of ageing across the tree of life., *Nature.* 505 (2014) 169–73. doi:10.1038/nature12789.
- [23] A.M. Valdes, D. Glass, T.D. Spector, Omics technologies and the study of human ageing., *Nat. Rev. Genet.* 14 (2013) 601–7. doi:10.1038/nrg3553.
- [24] B.M. Wasko, M. Kaeberlein, Yeast replicative aging: a paradigm for defining conserved longevity interventions, 14 (2014) 148–159. doi:10.1111/1567-1364.12104.
- [25] S.S. Lee, I.A. Vizcarra, D.H.E.W. Huberts, L.P. Lee, M. Heinemann, Whole lifespan microscopic observation of budding yeast aging through a microfluidic dissection platform, *Proc. Natl. Acad. Sci.* 109 (2012) 4916–4920. doi:10.1073/pnas.1113505109.

- [26] M.M. Crane, I.B.N. Clark, E. Bakker, S. Smith, P.S. Swain, A microfluidic system for studying ageing and dynamic single-cell responses in budding yeast, *PLoS One.* 9 (2014) 1–10. doi:10.1371/journal.pone.0100042.
- [27] G. Janssens, A. Meinema, J. González, J. Wolters, A. Schmidt, V. Guryev, et al., Protein Biogenesis Machinery is a Driver of Replicative Aging in Yeast, *eLife.* (2015). doi:10.7554/eLife.08527.
- [28] B.K. Kennedy, M. Kaeberlein, Hot topics in aging research: Protein translation, 2009, *Aging Cell.* 8 (2009) 617–623. doi:10.1111/j.1474-9726.2009.00522.x.
- [29] K.K. Steffen, V.L. MacKay, E.O. Kerr, M. Tsuchiya, D. Hu, L.A. Fox, et al., Yeast Life Span Extension by Depletion of 60S Ribosomal Subunits Is Mediated by Gcn4, *Cell.* 133 (2008) 292–302. doi:10.1016/j.cell.2008.02.037.
- [30] M. Kaeberlein, R.W. Powers, K.K. Steffen, E.A. Westman, D. Hu, N. Dang, et al., Regulation of yeast replicative life span by TOR and Sch9 in response to nutrients., *Science.* 310 (2005) 1193–1196. doi:10.1126/science.1115535.
- [31] S.C. Johnson, P.S. Rabinovitch, M. Kaeberlein, mTOR is a key modulator of ageing and age-related disease., *Nature.* 493 (2013) 338–45. doi:10.1038/nature11861.
- [32] D.H.E.W. Huberts, G.E. Janssens, S.S. Lee, I.A. Vizcarra, M. Heinemann, Continuous High-resolution Microscopic Observation of Replicative Aging in Budding Yeast., *J. Vis. Exp.* (2013) e50143. doi:10.3791/50143.
- [33] D.H.E.W. Huberts, S.S. Lee, J. González, G.E. Janssens, I.A. Vizcarra, M. Heinemann, Construction and use of a microfluidic dissection platform for long-term imaging of cellular processes in budding yeast., *Nat. Protoc.* 8 (2013) 1019–27. doi:10.1038/nprot.2013.060.
- [34] C. López-Otín, M.A. Blasco, L. Partridge, M. Serrano, G. Kroemer, XThe hallmarks of aging, *Cell.* 153 (2013). doi:10.1016/j.cell.2013.05.039.
- [35] A. Friede, J.A. Reid, H.W. Ory, CDC WONDER: a comprehensive on-line public health information system of the Centers for Disease Control and Prevention, *Am J Public Heal.* 83 (1993) 1289–1294. doi:10.2105/AJPH.83.9.1289.
- [36] D.H.E.W. Huberts, J. González, S.S. Lee, A. Litsios, G. Hubmann, E.C. Wit, et al., Calorie restriction does not elicit a robust extension of replicative lifespan in *Saccharomyces cerevisiae.*, *Proc. Natl. Acad. Sci. U. S. A.* 111 (2014) 11727–11731. doi:10.1073/pnas.1410024111.

Bibliography

- [37] J.P. de Magalhães, D. Wuttke, S.H. Wood, M. Plank, C. Vora, Genome-environment interactions that modulate aging: powerful targets for drug discovery., *Pharmacol. Rev.* 64 (2012) 88–101. doi:10.1124/pr.110.004499.
- [38] P.B. Medawar, An Unsolved Problem of Biology, *Evol. Heal. Dis.* (1952) 24.
- [39] M. A. McCormick, B. K. Kennedy, Genome-Scale Studies of Aging: Challenges and Opportunities, *Curr. Genomics.* 13 (2012) 500–507. doi:10.2174/138920212803251454.
- [40] A.E. Webb, A. Brunet, FOXO transcription factors: Key regulators of cellular quality control, *Trends Biochem. Sci.* 39 (2014) 159–169. doi:10.1016/j.tibs.2014.02.003.
- [41] M. Lagouge, N.-G. Larsson, The role of mitochondrial DNA mutations and free radicals in disease and ageing., *J. Intern. Med.* 273 (2013) 529–43. doi:10.1111/joim.12055.
- [42] N. Barzilai, D.M. Huffman, R.H. Muzumdar, A. Bartke, The critical role of metabolic pathways in aging, *Diabetes.* 61 (2012) 1315–1322. doi:10.2337/db11-1300.
- [43] R.K. Mortimer, J.R. Johnston, Life span of individual yeast cells., *Nature.* 183 (1959) 1751–1752. doi:10.1038/1831751a0.
- [44] A. Denoth-Lippuner, T. Julou, Y. Barral, Budding yeast as a model organism to study the effects of age, *FEMS Microbiol. Rev.* 38 (2014) 300–325. doi:10.1111/1574-6976.12060.
- [45] N.K. Egilmez, J.B. Chen, S.M. Jazwinski, Specific alterations in transcript prevalence during the yeast life span, *J. Biol. Chem.* 264 (1989) 14312–14317.
- [46] S.S. Lin, J.K. Manchester, J.I. Gordon, Enhanced Gluconeogenesis and Increased Energy Storage as Hallmarks of Aging in *Saccharomyces cerevisiae*, *J. Biol. Chem.* 276 (2001) 36000–36007. doi:10.1074/jbc.M103509200.
- [47] I. Lesur, J.L. Campbell, The transcriptome of prematurely aging yeast cells is similar to that of telomerase-deficient cells., *Mol. Biol. Cell.* 15 (2004) 1297–1312. doi:10.1091/mbc.E03-10-0742.
- [48] A. Koc, A.P. Gasch, J.C. Rutherford, H.-Y. Kim, V.N. Gladyshev, Methionine sulfoxide reductase regulation of yeast lifespan reveals reactive oxygen species-dependent and -independent components of aging., *Proc. Natl. Acad. Sci. U. S. A.* 101 (2004) 7999–8004. doi:10.1073/pnas.0307929101.

- [49] G. Yiu, A. McCord, A. Wise, R. Jindal, J. Hardee, A. Kuo, et al., Pathways change in expression during replicative aging in *Saccharomyces cerevisiae*., *J. Gerontol. A. Biol. Sci. Med. Sci.* 63 (2008) 21–34. doi:63/1/21 [pii].
- [50] T. Smeal, J. Claus, B. Kennedy, F. Cole, L. Guarente, Loss of transcriptional silencing causes sterility in old mother cells of *S. cerevisiae*, *Cell.* 84 (1996) 633–642. doi:10.1016/S0092-8674(00)81038-7.
- [51] N.K. Egilmez, J.B. Chen, S.M. Jazwinski, Preparation and partial characterization of old yeast cells., *J. Gerontol.* 45 (1990) B9–B17. doi:10.1093/geronj/45.1.B9.
- [52] C.D. Powell, D.E. Quain, K.A. Smart, Chitin scar breaks in aged *Saccharomyces cerevisiae*, *Microbiology.* 149 (2003) 3129–3137. doi:10.1099/mic.0.25940-0.
- [53] G.E. Janssens, A.C. Meinema, J. González, J.C. Wolters, A. Schmidt, V. Guryev, et al., Proteome data acquired during replicative aging of *S. cerevisiae*, (2015). doi:10.6019/PXD001714.
- [54] G.E. Janssens, A.C. Meinema, J. González, J.C. Wolters, A. Schmidt, V. Guryev, et al., Transcriptome data acquired during replicative aging of *S. cerevisiae*, (2015) EBI ArrayExpress accession E-MTAB-3605.
- [55] B.K. Kennedy, N.R. Austriaco, L. Guarente, Daughter cells of *Saccharomyces cerevisiae* from old mothers display a reduced life span, *J. Cell Biol.* 127 (1994) 1985–1993. doi:10.1083/jcb.127.6.1985.
- [56] S.F. Levy, N. Ziv, M.L. Siegal, Bet hedging in yeast by heterogeneous, age-correlated expression of a stress protectant, *PLoS Biol.* 10 (2012). doi:10.1371/journal.pbio.1001325.
- [57] N. Erjavec, L. Larsson, J. Grantham, T. Nyström, Accelerated aging and failure to segregate damaged proteins in Sir2 mutants can be suppressed by overproducing the protein aggregation-remodeling factor Hsp104p, *Genes Dev.* 21 (2007) 2410–2421. doi:10.1101/gad.439307.
- [58] A.L. Hughes, D.E. Gottschling, An early age increase in vacuolar pH limits mitochondrial function and lifespan in yeast., *Nature.* 492 (2012) 261–5. doi:10.1038/nature11654.
- [59] Y. Zhang, C. Luo, K. Zou, Z. Xie, O. Brandman, Q. Ouyang, et al., Single Cell Analysis of Yeast Replicative Aging Using a New Generation of Microfluidic Device, *PLoS One.* 7 (2012). doi:10.1371/journal.pone.0048275.

Bibliography

- [60] C.L. Lord, B.L. Timney, M.P. Rout, S.R. Wente, Altering nuclear pore complex function impacts longevity and mitochondrial function in *S. cerevisiae*, *J. Cell Biol.* 208 (2015) 729–744. doi:10.1083/jcb.201412024.
- [61] A. Denoth-Lippuner, M.K. Krzyzanowski, C. Stober, Y. Barral, Role of SAGA in the asymmetric segregation of DNA circles during yeast ageing, *eLife*. 3 (2014) 1–33. doi:10.7554/eLife.03790.
- [62] A. Eldakak, G. Rancati, B. Rubinstein, P. Paul, V. Conaway, R. Li, Asymmetrically inherited multidrug resistance transporters are recessive determinants in cellular replicative ageing., *Nat. Cell Biol.* 12 (2010) 799–805. doi:10.1038/ncb2085.
- [63] J. Sun, S.P. Kale, A.M. Childress, C. Pinswasdi, S.M. Jazwinski, Divergent roles of RAS1 and RAS2 in yeast longevity, *J. Biol. Chem.* 269 (1994) 18638–18645.
- [64] G. Csárdi, A. Franks, D.S. Choi, E.M. Airolidi, D.A. Drummond, Accounting for Experimental Noise Reveals That mRNA Levels , Amplified by Post-Transcriptional Processes , Largely Determine Steady-State Protein Levels in Yeast, (2015) 1–32. doi:10.5061/dryad.rg367.
- [65] R. Opgen-Rhein, K. Strimmer, From correlation to causation networks: a simple approximate learning algorithm and its application to high-dimensional plant gene expression data., *BMC Syst. Biol.* 1 (2007) 37. doi:10.1186/1752-0509-1-37.
- [66] G. Csardi, T. Nepusz, The igraph software package for complex network research, *InterJournal. Complex Sy* (2006) 1695. doi:citeulike-article-id:3443126.
- [67] D.H.E.W. Huberts, B. Niebel, M. Heinemann, A flux-sensing mechanism could regulate the switch between respiration and fermentation, *FEMS Yeast Res.* 12 (2012) 118–128. doi:10.1111/j.1567-1364.2011.00767.x.
- [68] J.M. Cherry, E.L. Hong, C. Amundsen, R. Balakrishnan, G. Binkley, E.T. Chan, et al., *Saccharomyces Genome Database: The genomics resource of budding yeast*, *Nucleic Acids Res.* 40 (2012). doi:10.1093/nar/gkr1029.
- [69] N.T. Ingolia, S. Ghaemmaghami, J.R.S. Newman, J.S. Weissman, Genome-wide analysis *in vivo* of translation with nucleotide resolution using ribosome profiling., *Science*. 324 (2009) 218–223. doi:10.1126/science.1168978.
- [70] A. Belle, A. Tanay, L. Bitincka, R. Shamir, E.K. O’Shea, Quantification of protein half-lives in the budding yeast proteome., *Proc. Natl. Acad. Sci. U. S. A.* 103 (2006) 13004–13009. doi:10.1073/pnas.0605420103.

- [71] P. Laun, A. Pichova, F. Madeo, J. Fuchs, A. Ellinger, S. Kohlwein, et al., Aged mother cells of *Saccharomyces cerevisiae* show markers of oxidative stress and apoptosis, *Mol. Microbiol.* 39 (2001) 1166–1173. doi:10.1046/j.1365-2958.2001.02317.x.
- [72] Z. Hu, K. Chen, Z. Xia, M. Chavez, S. Pal, J.H. Seol, et al., Nucleosome loss leads to global transcriptional up-regulation and genomic instability during yeast aging, *Genes Dev.* 28 (2014) 396–408. doi:10.1101/gad.233221.113.
- [73] A.M. Cuervo, Autophagy and aging: keeping that old broom working, *Trends Genet.* 24 (2008) 604–612. doi:10.1016/j.tig.2008.10.002.
- [74] P. Fabrizio, F. Pozza, S.D. Pletcher, C.M. Gendron, V.D. Longo, Regulation of longevity and stress resistance by Sch9 in yeast., *Science*. 292 (2001) 288–290. doi:10.1126/science.1059497.
- [75] T. Vellai, K. Takacs-Vellai, Y. Zhang, A.L. Kovacs, L. Orosz, F. Müller, Genetics: influence of TOR kinase on lifespan in *C. elegans*., *Nature*. 426 (2003) 620. doi:10.1038/426620a.
- [76] K.Z. Pan, J.E. Palter, A.N. Rogers, A. Olsen, D. Chen, G.J. Lithgow, et al., Inhibition of mRNA translation extends lifespan in *Caenorhabditis elegans*, *Aging Cell*. 6 (2007) 111–119. doi:10.1111/j.1474-9726.2006.00266.x.
- [77] P. Kapahi, B.M. Zid, T. Harper, D. Koslover, V. Sapin, S. Benzer, Regulation of lifespan in *Drosophila* by modulation of genes in the TOR signaling pathway, *Curr. Biol.* 14 (2004) 885–890. doi:10.1016/j.cub.2004.03.059.
- [78] D.W. Lamming, L. Ye, P. Katajisto, M.D. Goncalves, M. Saitoh, D.M. Stevens, et al., Rapamycin-Induced Insulin Resistance Is Mediated by mTORC2 Loss and Uncoupled from Longevity, *Science* (80-.). 335 (2012) 1638–1643. doi:10.1126/science.1215135.
- [79] C. Selman, J.M.A. Tullet, D. Wieser, E. Irvine, S.J. Lingard, A.I. Choudhury, et al., Ribosomal protein S6 kinase 1 signaling regulates mammalian life span., *Science*. 326 (2009) 140–144. doi:10.1126/science.1177221.
- [80] M. Hansen, S. Taubert, D. Crawford, N. Libina, S.J. Lee, C. Kenyon, Lifespan extension by conditions that inhibit translation in *Caenorhabditis elegans*, *Aging Cell*. 6 (2007) 95–110. doi:10.1111/j.1474-9726.2006.00267.x.
- [81] A.B. Canelas, N. Harrison, A. Fazio, J. Zhang, J.-P. Pitkänen, J. van den Brink, et al., Integrated multilaboratory systems biology reveals differences in protein metabolism between two reference yeast strains., *Nat. Commun.* 1 (2010) 145. doi:10.1038/ncomms1150.

Bibliography

- [82] C. Verduyn, E. Postma, W.A. Scheffers, J.P. Van Dijken, Effect of benzoic acid on metabolic fluxes in yeasts: A continuous-culture study on the regulation of respiration and alcoholic fermentation, *Yeast.* 8 (1992) 501–517. doi:10.1002/yea.320080703.
- [83] B. MacLean, D.M. Tomazela, N. Shulman, M. Chambers, G.L. Finney, B. Frewen, et al., Skyline: An open source document editor for creating and analyzing targeted proteomics experiments, *Bioinformatics.* 26 (2010) 966–968. doi:10.1093/bioinformatics/btq054.
- [84] T. Glatter, C. Ludwig, E. Ahrné, R. Aebersold, A.J.R. Heck, A. Schmidt, Large-scale quantitative assessment of different in-solution protein digestion protocols reveals superior cleavage efficiency of tandem Lys-C/trypsin proteolysis over trypsin digestion, *J. Proteome Res.* 11 (2012) 5145–5156. doi:10.1021/pr300273g.
- [85] External-RNA-Controls-Consortium, Proposed methods for testing and selecting the ERCC external RNA controls., *BMC Genomics.* 6 (2005) 150. doi:10.1186/1471-2164-6-150.
- [86] A. Zeileis, G. Grothendieck, ZOO: S3 Infrastructure for Regular and Irregular Time Series, *J. Stat. Softw.* 14 (2005) 1–27.
- [87] R. Core Development Team, R: A Language and Environment for Statistical Computing, (2014). <http://www.r-project.org/>.
- [88] D.W. Huang, B.T. Sherman, R.A. Lempicki, Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources., *Nat. Protoc.* 4 (2009) 44–57. doi:10.1038/nprot.2008.211.
- [89] I. Fellows, Word Clouds, R Packag. Version 2.5. (2014). <http://cran.r-project.org/package=wordcloud>.
- [90] A.A. Kalaitzis, N.D. Lawrence, A simple approach to ranking differentially expressed gene expression time courses through Gaussian process regression., *BMC Bioinformatics.* 12 (2011) 180. doi:10.1186/1471-2105-12-180.
- [91] J. Schaefer, R. Opgen-Rhein, K. Strimmer, GeneNet: Modeling and Inferring Gene Networks, (2015). <http://cran.r-project.org/package=GeneNet>.
- [92] M.E.J. Newman, Finding community structure in networks using the eigenvectors of matrices, *Phys. Rev. E - Stat. Nonlinear, Soft Matter Phys.* 74 (2006). doi:10.1103/PhysRevE.74.036104.
- [93] L.N. Trefethen, D. Bau III, Numerical linear algebra, 1997. doi:10.1137/1.9780898719574.

- [94] C.L. Lawson, R.J. Hanson, Solving least squares problems, 1995. doi:10.2307/2005340.
- [95] K.M. Mullen, I.H.M. van Stokkum, nnls: The Lawson-Hanson algorithm for non-negative least squares (NNLS), (2012). <http://cran.r-project.org/package=nnls>.
- [96] J. Schäfer, K. Strimmer, A shrinkage approach to large-scale covariance matrix estimation and implications for functional genomics., *Stat. Appl. Genet. Mol. Biol.* 4 (2005) Article32. doi:10.2202/1544-6115.1175.
- [97] S. Falcon, R. Gentleman, Using GOstats to test gene lists for GO term association, *Bioinformatics*. 23 (2007) 257–258. doi:10.1093/bioinformatics/btl567.
- [98] M. Carlson, org.Sc.sgd.db: Genome wide annotation for Yeast, (n.d.).
- [99] C.E. Finch, R.E. Tanzi, Genetics of aging, *Science* (80-.). 278 (1997) 407–411. doi:10.1126/science.278.5337.407.
- [100] S.L. Rea, D. Wu, J.R. Cypser, J.W. Vaupel, T.E. Johnson, A stress-sensitive reporter predicts longevity in isogenic populations of *Caenorhabditis elegans*., *Nat. Genet.* 37 (2005) 894–898. doi:10.1038/ng1608.
- [101] Z. Pincus, T. Smith-Vikos, F.J. Slack, MicroRNA predictors of longevity in *caenorhabditis elegans*, *PLoS Genet.* 7 (2011). doi:10.1371/journal.pgen.1002306.
- [102] J.R. Delaney, A. Chou, B. Olsen, D. Carr, C. Murakami, U. Ahmed, et al., End-of-life cell cycle arrest contributes to stochasticity of yeast replicative aging, *FEMS Yeast Res.* 13 (2013) 267–276. doi:10.1111/1567-1364.12030.
- [103] X. Manière, a. Krisko, F.X. Pellay, J.-M. Di Meglio, P. Hersen, I. Matic, High transcript levels of heat-shock genes are associated with shorter lifespan of *Caenorhabditis elegans*, *Exp. Gerontol.* 60 (2014) 12–17. doi:10.1016/j.exger.2014.09.005.
- [104] A.A. Barton, Some Aspects of Cell Division in *Saccharomyces cerevisiae*, *J. Gen. Microbiol.* 4 (1950) 84–86. doi:10.1099/00221287-4-1-84.
- [105] Z. Xie, Y. Zhang, K. Zou, O. Brandman, C. Luo, Q. Ouyang, et al., Molecular phenotyping of aging in single yeast cells using a novel microfluidic device, *Aging Cell.* 11 (2012) 599–606. doi:10.1111/j.1474-9726.2012.00821.x.
- [106] S. Fehrman, C. Paoletti, Y. Goulev, A. Ungureanu, H. Aguilaniu, G. Charvin, Aging yeast cells undergo a sharp entry into senescence unrelated to the loss of mitochondrial membrane potential, *Cell Rep.* 5 (2013) 1589–1599. doi:10.1016/j.celrep.2013.11.013.

Bibliography

- [107] F. Moretto, I. Sagot, B. Daignan-Fornier, B. Pinson, A pharmaco-epistasis strategy reveals a new cell size controlling pathway in yeast., *Mol. Syst. Biol.* 9 (2013) 707. doi:10.1038/msb.2013.60.
- [108] C. He, S.K. Tsuchiyama, Q.T. Nguyen, E.N. Plyusnina, S.R. Terrill, S. Sahibzada, et al., Enhanced Longevity by Ibuprofen, Conserved in Multiple Species, Occurs in Yeast through Inhibition of Tryptophan Import, *PLoS Genet.* 10 (2014) e1004860. doi:10.1371/journal.pgen.1004860.
- [109] A.R.D. Ganley, M. Breitenbach, B.K. Kennedy, T. Kobayashi, Yeast hypertrophy: Cause or consequence of aging? Reply to Bilinski et al, *FEMS Yeast Res.* 12 (2012) 267–268. doi:10.1111/j.1567-1364.2012.00796.x.
- [110] M. Kaeberlein, Hypertrophy and senescence factors in yeast aging. A reply to Bilinski et al., *FEMS Yeast Res.* 12 (2012) 269–270. doi:10.1111/j.1567-1364.2012.00798.x.
- [111] J. Yang, H. Dungrawala, H. Hua, A. Manukyan, L. Abraham, W. Lane, et al., Cell size and growth rate are major determinants of replicative lifespan., *Cell Cycle.* 10 (2011) 144–155. doi:10.4161/cc.10.1.14455.
- [112] T. Biliński, R. Zadrag-Tecza, G. Bartosz, Hypertrophy hypothesis as an alternative explanation of the phenomenon of replicative aging of yeast, *FEMS Yeast Res.* 12 (2012) 97–101. doi:10.1111/j.1567-1364.2011.00759.x.
- [113] R. Zadrag, M. Kwolek-Mirek, G. Bartosz, T. Bilinski, Relationship between the replicative age and cell volume in *Saccharomyces cerevisiae*, *Acta Biochim. Pol.* 53 (2006) 747–751. doi:20061338A [pii].
- [114] J.R. Delaney, C.J. Murakami, B. Olsen, B.K. Kennedy, M. Kaeberlein, Quantitative evidence for early life fitness defects from 32 longevity-associated alleles in yeast, *Cell Cycle.* 10 (2011) 156–165. doi:10.4161/cc.10.1.14457.
- [115] Z. Xie, K.A. Jay, D.L. Smith, Y. Zhang, Z. Liu, J. Zheng, et al., Early Telomerase Inactivation Accelerates Aging Independently of Telomere Length, *Cell.* 160 (2015) 928–939. doi:10.1016/j.cell.2015.02.002.
- [116] D. Rudra, J.R. Warner, What better measure than ribosome synthesis?, *Genes Dev.* 18 (2004) 2431–2436. doi:10.1101/gad.1256704.
- [117] P. Jorgensen, I. Rupeš, J.R. Sharom, L. Schneper, J.R. Broach, M. Tyers, A dynamic transcriptional network communicates growth potential to ribosome synthesis and critical cell size, *Genes Dev.* 18 (2004) 2491–2505. doi:10.1101/gad.1228804.
- [118] M.C. Jo, W. Liu, L. Gu, W. Dang, L. Qin, High-throughput analysis of yeast replicative aging using a microfluidic system, *Proc. Natl. Acad. Sci.* (2015) 201510328. doi:10.1073/pnas.1510328112.

- [119] J.M. Skotheim, S. Di Talia, E.D. Siggia, F.R. Cross, Positive feedback of G1 cyclins ensures coherent cell cycle entry., *Nature*. 454 (2008) 291–296. doi:10.1038/nature07118.
- [120] W.-K. Huh, J. V Falvo, L.C. Gerke, A.S. Carroll, R.W. Howson, J.S. Weissman, et al., Global analysis of protein localization in budding yeast., *Nature*. 425 (2003) 686–691. doi:10.1038/nature02026.
- [121] C.A. Schneider, W.S. Rasband, K.W. Eliceiri, NIH Image to ImageJ: 25 years of image analysis, *Nat. Methods*. 9 (2012) 671–675. doi:10.1038/nmeth.2089.
- [122] T. Therneau, A Package for Survival Analysis in S. R package version, *Survival* (Lond). (2012). <http://r-forge.r-project.org>.
- [123] G.R. Warnes, gplots: Various R programming tools for plotting data, *J. Phycol.* 33 (2012) 569–575. doi:10.1111/j.0022-3646.1997.00569.x.
- [124] Y. Xia, G.M. Whitesides, SOFT LITHOGRAPHY, *Annu. Rev. Mater. Sci.* 28 (1998) 153–184. doi:10.1146/annurev.matsci.28.1.153.
- [125] A. Mata, A.J. Fleischman, S. Roy, Fabrication of multi-layer SU-8 microstructures, *J. Micromechanics Microengineering*. 16 (2006) 276–284. doi:10.1088/0960-1317/16/2/012.
- [126] Y. Huang, B. Agrawal, P. a Clark, J.C. Williams, J.S. Kuo, Evaluation of cancer stem cell migration using compartmentalizing microfluidic devices and live cell imaging., *J. Vis. Exp.* (2011) e3297. doi:10.3791/3297.
- [127] C.Q. Scheckhuber, N. Erjavec, a Tinazli, a Hamann, T. Nyström, H.D. Osiewacz, Reducing mitochondrial fission results in increased life span and fitness of two fungal ageing models., *Nat. Cell Biol.* 9 (2007) 99–105. doi:10.1038/ncb1524.
- [128] K.A. Steinkraus, M. Kaeberlein, B.K. Kennedy, Replicative aging in yeast: the means to the end., *Annu. Rev. Cell Dev. Biol.* 24 (2008) 29–54. doi:10.1146/annurev.cellbio.23.090506.123509.
- [129] P. Fabrizio, V.D. Longo, The chronological life span of *Saccharomyces cerevisiae*., *Methods Mol. Biol.* 371 (2007) 89–95. doi:10.1007/978-1-59745-361-5_8.
- [130] V.D. Longo, G.S. Shadel, M. Kaeberlein, B. Kennedy, Replicative and chronological aging in *saccharomyces cerevisiae*, *Cell Metab.* 16 (2012) 18–31. doi:10.1016/j.cmet.2012.06.002.

Bibliography

- [131] P. Laun, L. Ramachandran, S. Jarolim, E. Herker, P. Liang, J. Wang, et al., A comparison of the aging and apoptotic transcriptome of *Saccharomyces cerevisiae*, in: FEMS Yeast Res., 2005: pp. 1261–1272. doi:10.1016/j.femsyr.2005.07.006.
- [132] I.M. Conboy, T.A. Rando, Heterochronic parabiosis for the study of the effects of aging on stem cells and their niches, 11 (2012) 2260–2267. doi:10.4161/cc.20437.
- [133] N.R. Austriaco, L.P. Guarente, Changes of telomere length cause reciprocal changes in the lifespan of mother cells in *Saccharomyces cerevisiae*., Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 9768–9772. doi:10.1073/pnas.94.18.9768.
- [134] S. Kim, B. Villeponteau, S.M. Jazwinski, Effect of replicative age on transcriptional silencing near telomeres in *Saccharomyces cerevisiae*., Biochem. Biophys. Res. Commun. 219 (1996) 370–376. doi:10.1006/bbrc.1996.0240.
- [135] N.P. D'Mello, S.M. Jazwinski, Telomere length constancy during aging of *Saccharomyces cerevisiae*, J. Bacteriol. 173 (1991) 6709–6713.
- [136] I. Müller, Parental age and the life-span of zygotes of *Saccharomyces cerevisiae*, Antonie Van Leeuwenhoek. 51 (1985) 1–10. doi:10.1007/BF00444223.
- [137] S.-C. Mei, C. Brenner, Calorie restriction-mediated replicative lifespan extension in yeast is non-cell autonomous., PLoS Biol. 13 (2015) e1002048. doi:10.1371/journal.pbio.1002048.
- [138] J. Vijg, Y. Suh, Genome instability and aging., Annu. Rev. Physiol. 75 (2013) 645–68. doi:10.1146/annurev-physiol-030212-183715.
- [139] G. FAILLA, The aging process and cancerogenesis., Ann. N. Y. Acad. Sci. 71 (1958) 1124–1140. doi:10.1111/j.1749-6632.1958.tb54674.x.
- [140] L. Szilard, On the nature of the aging process, (1958) 30–45. doi:10.1073/pnas.45.1.30.
- [141] J.H.J. Hoeijmakers, DNA damage, aging, and cancer., N. Engl. J. Med. 361 (2009) 1475–1485. doi:10.1056/NEJMra0804615.
- [142] A.A. Moskalev, M. V. Shaposhnikov, E.N. Plyusnina, A. Zhavoronkov, A. Budovsky, H. Yanai, et al., The role of DNA damage and repair in aging through the prism of Koch-like criteria, Ageing Res. Rev. 12 (2013) 661–684. doi:10.1016/j.arr.2012.02.001.

A system wide view of replicative aging in budding yeast

- [143] C.R. Burtner, B.K. Kennedy, Progeria syndromes and ageing: what is the connection?, *Nat. Rev. Mol. Cell Biol.* 11 (2010) 567–578. doi:10.1038/nrm2944.
- [144] R.D. Kolodner, C.D. Putnam, K. Myung, Maintenance of genome stability in *Saccharomyces cerevisiae*., *Science*. 297 (2002) 552–557. doi:10.1126/science.1075277.
- [145] M. McVey, M. Kaeberlein, H.A. Tissenbaum, L. Guarente, The short life span of *Saccharomyces cerevisiae* sgs1 and srs2 mutants is a composite of normal aging processes and mitotic arrest due to defective recombination, *Genetics*. 157 (2001) 1531–1542.
- [146] L.L.M. Hoopes, M. Budd, W. Choe, T. Weitao, J.L. Campbell, Mutations in DNA replication genes reduce yeast life span., *Mol. Cell. Biol.* 22 (2002) 4136–4146. doi:10.1128/MCB.22.12.4136-4146.2002.
- [147] M. a McMurray, D.E. Gottschling, An age-induced switch to a hyper-recombinational state., *Science*. 301 (2003) 1908–11. doi:10.1126/science.1087706.
- [148] S. Gravel, S.P. Jackson, Increased genome instability in aging yeast., *Cell*. 115 (2003) 1–2. <http://www.ncbi.nlm.nih.gov/pubmed/14531992>.
- [149] A. Kaya, A. V. Lobanov, V.N. Gladyshev, Evidence that mutation accumulation does not cause aging in *Saccharomyces cerevisiae*, *Aging Cell*. (2014). doi:10.1111/acel.12290.
- [150] D.A. Sinclair, L. Guarente, Extrachromosomal rDNA circles - A cause of aging in yeast, *Cell*. 91 (1997) 1033–1042. doi:10.1016/S0092-8674(00)80493-6.
- [151] P.A. Defossez, R. Prusty, M. Kaeberlein, S.J. Lin, P. Ferrigno, P.A. Silver, et al., Elimination of replication block protein Fob1 extends the life span of yeast mother cells, *Mol. Cell*. 3 (1999) 447–455. doi:10.1016/S1097-2765(00)80472-4.
- [152] A.A. Falcón, J.P. Aris, Plasmid accumulation reduced life span in *Saccharomyces cerevisiae*, *J. Biol. Chem.* 278 (2003) 41607–41617. doi:10.1074/jbc.M307025200.
- [153] T. Kobayashi, A new role of the rDNA and nucleolus in the nucleus - RDNA instability maintains genome integrity, *BioEssays*. 30 (2008) 267–272. doi:10.1002/bies.20723.
- [154] A.R.D. Ganley, S. Ide, K. Saka, T. Kobayashi, The Effect of Replication Initiation on Gene Amplification in the rDNA and Its Relationship to Aging, *Mol. Cell*. 35 (2009) 683–693. doi:10.1016/j.molcel.2009.07.012.

B

Bibliography

- [155] K. Saka, S. Ide, A.R.D. Ganley, T. Kobayashi, Cellular senescence in yeast is regulated by rDNA noncoding transcription, *Curr. Biol.* 23 (2013) 1794–1798. doi:10.1016/j.cub.2013.07.048.
- [156] E.X. Kwan, E.J. Foss, S. Tsuchiyama, G.M. Alvino, L. Kruglyak, M. Kaeberlein, et al., A natural polymorphism in rDNA replication origins links origin activation with calorie restriction and lifespan., *PLoS Genet.* 9 (2013) e1003329. doi:10.1371/journal.pgen.1003329.
- [157] A.R.D. Ganley, T. Kobayashi, Ribosomal DNA and cellular senescence: New evidence supporting the connection between rDNA and aging, *FEMS Yeast Res.* 14 (2014) 49–59. doi:10.1111/1567-1364.12133.
- [158] R. Sweeney, V.A. Zakian, Extrachromosomal elements cause a reduced division potential in nib 1 strains of *Saccharomyces cerevisiae*., *Genetics*. 122 (1989) 749–757.
- [159] B. Sarg, E. Koutzamani, W. Helliger, I. Rundquist, H.H. Lindner, Postsynthetic trimethylation of histone H4 at lysine 20 in mammalian tissues is associated with aging, *J. Biol. Chem.* 277 (2002) 39195–39201. doi:10.1074/jbc.M205166200.
- [160] I. Cheung, H.P. Shulha, Y. Jiang, A. Matevossian, J. Wang, Z. Weng, et al., Developmental regulation and individual differences of neuronal H3K4me3 epigenomes in the prefrontal cortex., *Proc. Natl. Acad. Sci. U. S. A.* 107 (2010) 8824–8829. doi:10.1073/pnas.1001702107.
- [161] M.F. Fraga, M. Esteller, Epigenetics and aging: the targets and the marks, *Trends Genet.* 23 (2007) 413–418. doi:10.1016/j.tig.2007.05.008.
- [162] S. Han, A. Brunet, Histone methylation makes its mark on longevity, *Trends Cell Biol.* 22 (2012) 42–49. doi:10.1016/j.tcb.2011.11.001.
- [163] E.L. Greer, T.J. Maures, A.G. Hauswirth, E.M. Green, D.S. Leeman, G.S. Maro, et al., Members of the H3K4 trimethylation complex regulate lifespan in a germline-dependent manner in *C. elegans*., *Nature*. 466 (2010) 383–387. doi:10.1038/nature09195.
- [164] A.P. Siebold, R. Banerjee, F. Tie, D.L. Kiss, J. Moskowitz, P.J. Harte, Polycomb Repressive Complex 2 and Trithorax modulate *Drosophila* longevity and stress resistance., *Proc. Natl. Acad. Sci. U. S. A.* 107 (2010) 169–174. doi:10.1073/pnas.0907739107.
- [165] C. Jin, J. Li, C.D. Green, X. Yu, X. Tang, D. Han, et al., Histone demethylase UTX-1 regulates *C. elegans* life span by targeting the insulin/IGF-1 signaling pathway, *Cell Metab.* 14 (2011) 161–172. doi:10.1016/j.cmet.2011.07.001.

A system wide view of replicative aging in budding yeast

- [166] R.E. Marioni, S. Shah, A.F. McRae, B.H. Chen, E. Colicino, S.E. Harris, et al., DNA methylation age of blood predicts all-cause mortality in later life, *Genome Biol.* 16 (2015) 1–12. doi:10.1186/s13059-015-0584-6.
- [167] M.J. Jones, S.J. Goodman, M.S. Kobor, DNA methylation and healthy human aging, *Aging Cell.* (2015) n/a–n/a. doi:10.1111/acel.12349.
- [168] M. Kaeberlein, M. McVey, L. Guarente, The SIR2/3/4 complex and SIR2 alone promote longevity in *Saccharomyces cerevisiae* by two different mechanisms, *Genes Dev.* 13 (1999) 2570–2580. doi:10.1101/gad.13.19.2570.
- [169] L. Guarente, Sirtuins, aging, and metabolism, *Cold Spring Harb. Symp. Quant. Biol.* 76 (2011) 81–90. doi:10.1101/sqb.2011.76.010629.
- [170] W. Dang, K.K. Steffen, R. Perry, J.A. Dorsey, F.B. Johnson, A. Shilatifard, et al., Histone H4 lysine 16 acetylation regulates cellular lifespan., *Nature.* 459 (2009) 802–807. doi:10.1038/nature08085.
- [171] N. Suka, K. Luo, M. Grunstein, Sir2p and Sas2p opposingly regulate acetylation of yeast histone H4 lysine16 and spreading of heterochromatin, *Nat Genet.* 32 (2002) 378–383. doi:10.1038/ng1017\ng1017 [pii].
- [172] M.A. McCormick, A.G. Mason, S.J. Guyenet, W. Dang, R.M. Garza, M.K. Ting, et al., The SAGA Histone Deubiquitinase Module Controls Yeast Replicative Lifespan via Sir2 Interaction, *Cell Rep.* 8 (2014) 477–486. doi:10.1016/j.celrep.2014.06.037.
- [173] J. Feser, D. Truong, C. Das, J.J. Carson, J. Kieft, T. Harkness, et al., Elevated Histone Expression Promotes Life Span Extension, *Mol. Cell.* 39 (2010) 724–735. doi:10.1016/j.molcel.2010.08.015.
- [174] F. Capuano, M. Mülleder, R. Kok, H.J. Blom, M. Ralser, Cytosine DNA methylation is found in *drosophila melanogaster* but absent in *saccharomyces cerevisiae*, *schizosaccharomyces pombe*, and other yeast species, *Anal. Chem.* 86 (2014) 3697–3702. doi:10.1021/ac500447w.
- [175] I. Saez, D. Vilchez, The Mechanistic Links Between Proteasome Activity, Aging and Age-related Diseases., *Curr. Genomics.* 15 (2014) 38–51. doi:10.2174/138920291501140306113344.
- [176] H. Koga, S. Kaushik, A.M. Cuervo, Protein Homeostasis and Aging: the importance of exquisite quality control, *Ageing Res. Rev.* 10 (2012) 205–215. doi:10.1016/j.arr.2010.02.001.Protein.
- [177] S.K. Calderwood, A. Murshid, T. Prince, The shock of aging: Molecular chaperones and the heat shock response in longevity and aging - A mini-review, *Gerontology.* 55 (2009) 550–558. doi:10.1159/000225957.

Bibliography

- [178] G. Morrow, M. Samson, S. Michaud, R.M. Tanguay, Overexpression of the small mitochondrial Hsp22 extends *Drosophila* life span and increases resistance to oxidative stress., *FASEB J.* 18 (2004) 598–599. doi:10.1096/fj.03-0860fje.
- [179] G.A. Walker, G.J. Lithgow, Lifespan extension in *C. elegans* by a molecular chaperone dependent upon insulin-like signals., *Aging Cell.* 2 (2003) 131–139. doi:10.1046/j.1474-9728.2003.00045.x.
- [180] W.C. Chiang, T.T. Ching, H.C. Lee, C. Mousigian, A.L. Hsu, HSF-1 regulators DDL-1/2 link insulin-like signaling to heat-shock responses and modulation of longevity, *Cell.* 148 (2012) 322–334. doi:10.1016/j.cell.2011.12.019.
- [181] A.-L. Hsu, C.T. Murphy, C. Kenyon, Regulation of aging and age-related disease by DAF-16 and heat-shock factor., *Science.* 300 (2003) 1142–1145. doi:10.1126/science.1083701.
- [182] J.-O. Pyo, S.-M. Yoo, H.-H. Ahn, J. Nah, S.-H. Hong, T.-I. Kam, et al., Overexpression of Atg5 in mice activates autophagy and extends lifespan., *Nat. Commun.* 4 (2013) 2300. doi:10.1038/ncomms3300.
- [183] G. Reverter-Branchat, E. Cabiscol, J. Tamarit, J. Ros, Oxidative damage to specific proteins in replicative and chronological-aged *Saccharomyces cerevisiae*. Common targets and prevention by calorie restriction, *J. Biol. Chem.* 279 (2004) 31983–31989. doi:10.1074/jbc.M404849200.
- [184] H. Aguilaniu, L. Gustafsson, M. Rigoulet, T. Nyström, Asymmetric inheritance of oxidatively damaged proteins during cytokinesis., *Science.* 299 (2003) 1751–1753. doi:10.1126/science.1080418.
- [185] E. Unal, B. Kinde, A. Amon, Gametogenesis eliminates age-induced cellular damage and resets life span in yeast., *Science.* 332 (2011) 1554–1557. doi:10.1126/science.1204349.
- [186] M. Kaeberlein, K.T. Kirkland, S. Fields, B.K. Kennedy, Genes determining yeast replicative life span in a long-lived genetic background, *Mech. Ageing Dev.* 126 (2005) 491–504. doi:10.1016/j.mad.2004.10.007.
- [187] V. Andersson, S. Hanzén, B. Liu, M. Molin, T. Nyström, Enhancing protein disaggregation restores proteasome activity in aged cells, *Aging (Albany, NY).* 5 (2013) 802–812.
- [188] U. Kruegel, B. Robison, T. Dange, G. Kahlert, J.R. Delaney, S. Kotireddy, et al., Elevated proteasome capacity extends replicative lifespan in *saccharomyces cerevisiae*, *PLoS Genet.* 7 (2011). doi:10.1371/journal.pgen.1002253.

A system wide view of replicative aging in budding yeast

- [189] Y. Kamei, Y. Tamada, Y. Nakayama, E. Fukusaki, Y. Mukai, Changes in transcription and metabolism during the early stage of replicative cellular senescence in budding yeast., *J. Biol. Chem.* 289 (2014) 32081–93. doi:10.1074/jbc.M114.600528.
- [190] S.D.L. Postnikoff, M.E. Malo, B. Wong, T.A.A. Harkness, The yeast forkhead transcription factors fkh1 and fkh2 regulate lifespan and stress response together with the anaphase-promoting complex, *PLoS Genet.* 8 (2012). doi:10.1371/journal.pgen.1002583.
- [191] D. Harman, Aging: a theory based on free radical and radiation chemistry., *J. Gerontol.* 11 (1956) 298–300. doi:10.1093/geronj/11.3.298.
- [192] D.R. Green, L. Galluzzi, G. Kroemer, Mitochondria and the autophagy-inflammation-cell death axis in organismal aging., *Science.* 333 (2011) 1109–1112. doi:10.1126/science.1201940.
- [193] K. Wang, D.J. Klionsky, Mitochondria removal by autophagy, *Autophagy.* 7 (2011) 297–300. doi:10.4161/auto.7.3.14502.
- [194] M. Breitenbach, M. Rinnerthaler, J. Hartl, A. Stincone, J. Vowinkel, H. Breitenbach-Koller, et al., Mitochondria in ageing: There is metabolism beyond the ROS, *FEMS Yeast Res.* 14 (2014) 198–212. doi:10.1111/1567-1364.12134.
- [195] J.R. McFaline-Figueroa, J. Vevea, T.C. Swayne, C. Zhou, C. Liu, G. Leung, et al., Mitochondrial quality control during inheritance is associated with lifespan and mother-daughter age asymmetry in budding yeast, *Aging Cell.* 10 (2011) 885–895. doi:10.1111/j.1474-9726.2011.00731.x.
- [196] J.R. Veatch, M.A. McMurray, Z.W. Nelson, D.E. Gottschling, Mitochondrial Dysfunction Leads to Nuclear Genome Instability via an Iron-Sulfur Cluster Defect, *Cell.* 137 (2009) 1247–1258. doi:10.1016/j.cell.2009.04.014.
- [197] P.A. Kirchman, S. Kim, C.Y. Lai, S. Michal Jazwinski, Interorganelle signaling is a determinant of longevity in *Saccharomyces cerevisiae*, *Genetics.* 152 (1999) 179–190.
- [198] J. Yang, M. a McCormick, J. Zheng, Z. Xie, M. Tsuchiya, S. Tsuchiyama, et al., Systematic analysis of asymmetric partitioning of yeast proteome between mother and daughter cells reveals “aging factors” and mechanism of lifespan asymmetry, *112* (2015). doi:10.1073/pnas.1506054112.
- [199] F. Tang, J.W. Watkins, M. Bermudez, R. Gray, A. Gaban, K. Portie, et al., A life-span extending form of autophagy employs the vacuole-vacuole fusion machinery, *Autophagy.* 4 (2008) 874–886. doi:6556 [pii].

B

Bibliography

- [200] M. Boselli, J. Rock, E. Ünal, S.S. Levine, A. Amon, Effects of Age on Meiosis in Budding Yeast, *Dev. Cell.* 16 (2009) 844–855. doi:10.1016/j.devcel.2009.05.013.
- [201] S.M. Jazwinski, S. Kim, C.Y. Lai, A. Benguria, Epigenetic stratification: the role of individual change in the biological aging process., *Exp. Gerontol.* 33 (1998) 571–580. doi:10.1016/S0531-5565(98)00029-1.
- [202] S.P. Kale, S.M. Jazwinski, Differential response to UV stress and DNA damage during the yeast replicative life span, *Dev. Genet.* 18 (1996) 154–160. doi:10.1002/(SICI)1520-6408(1996)18:2<154::AID-DVG8>3.0.CO;2-8.
- [203] S.J. Lin, P.A. Defossez, L. Guarente, Requirement of NAD and SIR2 for life-span extension by calorie restriction in *Saccharomyces cerevisiae.*, *Science.* 289 (2000) 2126–2128. doi:10.1126/science.289.5487.2126.
- [204] J.W. Bartholomew, T. Mittwer, Demonstration of yeast bud scars with the electron microscope, *J. Bacteriol.* 65 (1953) 272–275.

B