Cell, Volume *36*

Supplemental Information

Epigenetic Mechanisms of Longevity and Aging

Payel Sen, Parisha P. Shah, Raffaella Nativio, and Shelley L. Berger

Supplemental Table 1: Epigenetic pathways of aging and longevity in different model organisms				
Models	***Epigenetic changes linked to aging***	***Physiological consequence***	***Experimental intervention to improve longevity/healthspan***	***Reference***
Yeast (replicative lifespan)	Canonical histone loss	Transcriptional amplification	Overexpression of histones	(Feser et al., 2010)
	Decrease in Sir2	Loss of heterochromatin at subtelomeric and rDNA loci, increase of H4K16ac and accumulation of ERCs	Overexpression of *SIR2*, deletion of *SAS2*, resveratrol and STACs	(Dang et al., 2009; Kaeberlein et al., 1999; Kim et al., 1999)
	Increased occupancy of chromatin remodeling complex RSC genome-wide upon rapamycin treatment	Downregulation of TORC1 signaling	Rapamycin treatment, calorie restriction	(Damelin et al., 2002)
	Release of Esa1 binding from RP promoters upon nutrient starvation or rapamycin treatment, reduced H3K56ac globally and locally at rDNA loci upon rapamycin treatment			(Chen et al., 2012; Rohde and Cardenas, 2003)
	Loss of H3K36me3 in a subset of genes	Upregulation of cryptic transcription	Deletion of *RPH1*	(Sen et al., 2015)
	Upregulation of stress response genes upon deletion of *ISW2*	Calorie restriction, stress response	Deletion of *ISW2*, calorie restriction	(Dang et al., 2014)
Yeast (chronological lifespan)	Gene expression changes induced by deletion of *RAS2* via stress response transcription factors	Calorie restriction, Ras/AC/PKA pathway, stress response	Deletion of *RAS2*	(Fabrizio et al., 2003; Longo, 1999; Pedruzzi et al., 2000)
	Mitochondria to nucleus signaling and Rph1-mediated chromatin changes	Hormetic response of mtROS		(Schroeder et al., 2013)
Worm	DAF-16-mediated recruitment of SWI/SNF	Stress resistance, dauer formation and longevity through the insulin signaling pathway		(Riedel et al., 2013)
	Possible histone acetylation by TOR at ribosomal protein genes	Activation of TOR pathway	Rapamycin treatment	(Wullschleger et al., 2006)
	Possible SIR-2.1 mediated deacetylation of histones	Consequences of calorie restriction	SIR-2.1 overexpression, boosting NAD+ levels by calorie restriction, treatment with PARP enzyme inhibitors	(Tissenbaum and Guarente, 2001)
	Chromatin remodeling by worm ISW2 component ATHP2, possibly also upregulating stress response genes upon deletion	Consequences of calorie restriction	RNAi of *athp-2*, calorie restriction	(Dang et al., 2014)
	Changes in H3K4me3	Transcription	RNAi of	(Greer et al., 2010)

		upregulation	methyltransferase subunits or overexpression of *rbr-2* demethylase affecting H3K4me3	
	Changes in H3K27me3 (down globally) in somatic cells	Insulin signaling pathway	RNAi of *utx-1* demethylase	(Maures et al., 2011)
	Possible loss of H3K36me3 in a subset of genes	Upregulation of cryptic transcription	RNAi of *RPH1* homolog *jmjd-2* and methyl binders F15E6.1 and T09A5.8	(Sen et al., 2015)
	Global loss of H3K36me3 upon reduction of *met-1*	Gene expression variation during aging and shorter lifespan	Unknown	(Pu et al., 2015)
	DNA methylation on N6 adenine (6mA)	Unknown	Unknown	(Greer et al., 2015)
Fly	Upregulation of *Sir2* and downregulation of *Rpd3*	Lifespan extension upon calorie restriction	Overexpression of *Sir2*, RNAi of *Rpd3*, HDAC inhibitors although dosage and time of administration must be tightly controlled to observe longevity effects	(Rogina et al., 2002; Wood et al., 2004)
	Overexpression/downregulation of *Lid*	Lifespan extension/ lifespan reduction by changing H3K4me3 global levels	Overexpression of *Lid* demethylase	(Li et al., 2010)
	Mutations in PRC2 subunits *E(z)* and *esc*	Lifespan extension through H3K27me3 global downregulation	RNAi of PRC2 components *E(z)* and *esc*	(Siebold et al., 2010)
	Mutations in *trx*	Suppression of longevity phenotype on the *E(z)* mutants through increase in H3K27me3	Mutating *trx* in *E(z)* mutants	
	Overexpression of DNA methyltransferase *Dnmt2*	Lifespan extension through CpG methylation	Overexpression of *Dnmt2*	(Lin et al., 2005)
Killifish	Upregulation of H3K27me3	Upregulation of ribosome, lysosome and complement activation genes. downregulation of synapse, mitochondria, proteasome and spliceosome genes		(Baumgart et al., 2014)
Normal mouse	Increase of macroH2A with age	Age-associated gain		(Kreiling et al.,

	Increase in HP1b with age	in heterochromatin		2011)
	Increase in H4K20me3 (rat)			(Sarg et al., 2002)
	Overexpression of *Sirt1*	Increased health benefits (lower levels of DNA damage, fewer spontaneous carcinomas and sarcomas) but not longevity		(Herranz et al., 2010; Libert and Guarente, 2013)
	Overexpression of neuronal *Sirt1*	Lifespan extension and delayed aging		(Satoh et al., 2013)
	Overexpression of *Sirt6* (H3K9 and H3K56 deacetylation)	Maximum lifespan increase in male mice		(Kanfi et al., 2012)
Long-lived dwarf mouse models	Reduced levels of DNMT1 in Ames mice liver	Lifespan extension/growth retardation through the IGF1 pathway		(Armstrong et al., 2014)
Premature aging mouse models	Hypermethylation at rDNA and hypoacetylation on core histones H4 and H2B in *Zmpste24* mice	Premature aging and age-related pathologies: deregulation of lamin A network		(Oakes et al., 2003; Osorio et al., 2010)
	BUBR1 (acetylated by CBP and deacetylated by SIRT2) deficient mice	Reduced lifespan, accelerated onset of age-related pathologies and accumulation of senescent cells (mitotic checkpoint response)	Overexpression *Sirt2* or treatment with NAD+	(Corrigan et al., 2005)
	Overexpression of *Sirt2* or NAD+ precursor treatment in *BubR1* mutant mice	Increased BUBR1 levels and median lifespan		(North et al., 2014)
Senescent cell cultures	Increase in H3K9me3, H3K27me3, HMGA	Formation of SAHF		(Chandra et al., 2012)
	Loss of EZH2 and H3K27me3	Upregulation of p16INK4a		(Bracken et al., 2007)
	Loss of Lamin B1	Transcriptional downregulation and autophagic degradation of Lamin B1 with possible nuclear disorganization		(Dou et al., 2015; Shimi et al., 2011)
	Gains in H3K4me3 and H3K27me3 over LAD and loss of H3K27me3 outside LAD	Activation of SASP genes and downregulation of cell-cycle genes		(Shah et al., 2013)
	Gains in H4K16ac at promoters of expressed genes mediated by HIRA	Dynamic chromatin state with the maintenance of		(Rai et al., 2014)

		H4K16ac in senescent cells		
	H3.3 in PML bodies	Formation of SAHF		
	Knockdown of *BAZ1A*	Upregulation of stress response genes		(Dang et al., 2014)
Stem cells	Broadening of H3K4me3 and H3K27me3 peaks, upregulated expression of repeat elements	Reduction in TGFβ signaling and myeloid differentiation (HSC)		(Sun et al., 2014)
Tissues	Accumulation of macroH2A and HP1b in aging mouse and primate tissue	Gain of heterochromatin		(Herbig et al., 2006; Kreiling et al., 2011)
	Promoter hypermethylation and global hypomethylation			(Day et al., 2013)
	Methylation clock			(Horvath, 2013, 2015)
	Rate of change of the DNA methylome from human blood			(Hannum et al., 2013)

References

Armstrong, V.L., Rakoczy, S., Rojanathammanee, L., and Brown-Borg, H.M. (2014). Expression of DNA methyltransferases is influenced by growth hormone in the long-living Ames dwarf mouse in vivo and in vitro. J Gerontol A Biol Sci Med Sci *69*, 923-933.

Baumgart, M., Groth, M., Priebe, S., Savino, A., Testa, G., Dix, A., Ripa, R., Spallotta, F., Gaetano, C., Ori, M.*, et al.* (2014). RNA-seq of the aging brain in the short-lived fish N. furzeri - conserved pathways and novel genes associated with neurogenesis. Aging Cell *13*, 965-974.

Bracken, A.P., Kleine-Kohlbrecher, D., Dietrich, N., Pasini, D., Gargiulo, G., Beekman, C., Theilgaard-Monch, K., Minucci, S., Porse, B.T., Marine, J.C.*, et al.* (2007). The Polycomb group proteins bind throughout the INK4A-ARF locus and are disassociated in senescent cells. Genes Dev *21*, 525-530.

Chandra, T., Kirschner, K., Thuret, J.Y., Pope, B.D., Ryba, T., Newman, S., Ahmed, K., Samarajiwa, S.A., Salama, R., Carroll, T.*, et al.* (2012). Independence of repressive histone marks and chromatin compaction during senescent heterochromatic layer formation. Mol Cell *47*, 203-214.

Chen, H., Fan, M., Pfeffer, L.M., and Laribee, R.N. (2012). The histone H3 lysine 56 acetylation pathway is regulated by target of rapamycin (TOR) signaling and functions directly in ribosomal RNA biogenesis. Nucleic Acids Res *40*, 6534-6546.

Corrigan, D.P., Kuszczak, D., Rusinol, A.E., Thewke, D.P., Hrycyna, C.A., Michaelis, S., and Sinensky, M.S. (2005). Prelamin A endoproteolytic processing in vitro by recombinant Zmpste24. Biochem J *387*, 129-138.

Damelin, M., Simon, I., Moy, T.I., Wilson, B., Komili, S., Tempst, P., Roth, F.P., Young, R.A., Cairns, B.R., and Silver, P.A. (2002). The genome-wide localization of Rsc9, a component of the RSC chromatin-remodeling complex, changes in response to stress. Mol Cell *9*, 563-573.

Dang, W., Steffen, K.K., Perry, R., Dorsey, J.A., Johnson, F.B., Shilatifard, A., Kaeberlein, M., Kennedy, B.K., and Berger, S.L. (2009). Histone H4 lysine 16 acetylation regulates cellular lifespan. Nature *459*, 802-807.

Dang, W., Sutphin, G.L., Dorsey, J.A., Otte, G.L., Cao, K., Perry, R.M., Wanat, J.J., Saviolaki, D., Murakami, C.J., Tsuchiyama, S.*, et al.* (2014). Inactivation of yeast Isw2 chromatin remodeling enzyme mimics longevity effect of calorie restriction via induction of genotoxic stress response. Cell Metab *19*, 952-966.

Day, K., Waite, L.L., Thalacker-Mercer, A., West, A., Bamman, M.M., Brooks, J.D., Myers, R.M., and Absher, D. (2013). Differential DNA methylation with age displays both common and dynamic features across human tissues that are influenced by CpG landscape. Genome Biol *14*, R102.

Dou, Z., Xu, C., Donahue, G., Shimi, T., Pan, J.A., Zhu, J., Ivanov, A., Capell, B.C., Drake, A.M., Shah, P.P.*, et al.* (2015). Autophagy mediates degradation of nuclear lamina. Nature.

Fabrizio, P., Liou, L.L., Moy, V.N., Diaspro, A., Valentine, J.S., Gralla, E.B., and Longo, V.D. (2003). SOD2 functions downstream of Sch9 to extend longevity in yeast. Genetics *163*, 35-46.
Feser, J., Truong, D., Das, C., Carson, J.J., Kieft, J., Harkness, T., and Tyler, J.K. (2010). Elevated histone expression promotes life span extension. Mol Cell *39*, 724-735.
Greer, E.L., Blanco, M.A., Gu, L., Sendinc, E., Liu, J., Aristizabal-Corrales, D., Hsu, C.H., Aravind, L., He, C., and Shi, Y. (2015). DNA Methylation on N6-Adenine in C. elegans. Cell *161*, 868-878.
Greer, E.L., Maures, T.J., Hauswirth, A.G., Green, E.M., Leeman, D.S., Maro, G.S., Han, S., Banko, M.R., Gozani, O., and Brunet, A. (2010). Members of the H3K4 trimethylation complex regulate lifespan in a germline-dependent manner in C. elegans. Nature *466*, 383-387.
Hannum, G., Guinney, J., Zhao, L., Zhang, L., Hughes, G., Sadda, S., Klotzle, B., Bibikova, M., Fan, J.B., Gao, Y.*, et al.* (2013). Genome-wide methylation profiles reveal quantitative views of human aging rates. Mol Cell *49*, 359-367.
Herbig, U., Ferreira, M., Condel, L., Carey, D., and Sedivy, J.M. (2006). Cellular senescence in aging primates. Science *311*, 1257.
Herranz, D., Munoz-Martin, M., Canamero, M., Mulero, F., Martinez-Pastor, B., Fernandez-Capetillo, O., and Serrano, M. (2010). Sirt1 improves healthy ageing and protects from metabolic syndrome-associated cancer. Nat Commun *1*, 3.
Horvath, S. (2013). DNA methylation age of human tissues and cell types. Genome Biol *14*, R115.
Horvath, S. (2015). Erratum to: DNA methylation age of human tissues and cell types. Genome Biol *16*, 96.
Kaeberlein, M., McVey, M., and Guarente, L. (1999). The SIR2/3/4 complex and SIR2 alone promote longevity in Saccharomyces cerevisiae by two different mechanisms. Genes Dev *13*, 2570-2580.
Kanfi, Y., Naiman, S., Amir, G., Peshti, V., Zinman, G., Nahum, L., Bar-Joseph, Z., and Cohen, H.Y. (2012). The sirtuin SIRT6 regulates lifespan in male mice. Nature *483*, 218-221.
Kim, S., Benguria, A., Lai, C.Y., and Jazwinski, S.M. (1999). Modulation of life-span by histone deacetylase genes in Saccharomyces cerevisiae. Mol Biol Cell *10*, 3125-3136.
Kreiling, J.A., Tamamori-Adachi, M., Sexton, A.N., Jeyapalan, J.C., Munoz-Najar, U., Peterson, A.L., Manivannan, J., Rogers, E.S., Pchelintsev, N.A., Adams, P.D.*, et al.* (2011). Age-associated increase in heterochromatic marks in murine and primate tissues. Aging Cell *10*, 292-304.
Li, L., Greer, C., Eisenman, R.N., and Secombe, J. (2010). Essential functions of the histone demethylase lid. PLoS Genet *6*, e1001221.
Libert, S., and Guarente, L. (2013). Metabolic and neuropsychiatric effects of calorie restriction and sirtuins. Annu Rev Physiol *75*, 669-684.
Lin, M.J., Tang, L.Y., Reddy, M.N., and Shen, C.K. (2005). DNA methyltransferase gene dDnmt2 and longevity of Drosophila. J Biol Chem *280*, 861-864.
Longo, V.D. (1999). Mutations in signal transduction proteins increase stress resistance and longevity in yeast, nematodes, fruit flies, and mammalian neuronal cells. Neurobiol Aging *20*, 479-486.
Maures, T.J., Greer, E.L., Hauswirth, A.G., and Brunet, A. (2011). The H3K27 demethylase UTX-1 regulates C. elegans lifespan in a germline-independent, insulin-dependent manner. Aging Cell *10*, 980-990.
North, B.J., Rosenberg, M.A., Jeganathan, K.B., Hafner, A.V., Michan, S., Dai, J., Baker, D.J., Cen, Y., Wu, L.E., Sauve, A.A.*, et al.* (2014). SIRT2 induces the checkpoint kinase BubR1 to increase lifespan. EMBO J *33*, 1438-1453.
Oakes, C.C., Smiraglia, D.J., Plass, C., Trasler, J.M., and Robaire, B. (2003). Aging results in hypermethylation of ribosomal DNA in sperm and liver of male rats. Proc Natl Acad Sci U S A *100*, 1775-1780.
Osorio, F.G., Varela, I., Lara, E., Puente, X.S., Espada, J., Santoro, R., Freije, J.M., Fraga, M.F., and Lopez-Otin, C. (2010). Nuclear envelope alterations generate an aging-like epigenetic pattern in mice deficient in Zmpste24 metalloprotease. Aging Cell *9*, 947-957.
Pedruzzi, I., Burckert, N., Egger, P., and De Virgilio, C. (2000). Saccharomyces cerevisiae Ras/cAMP pathway controls post-diauxic shift element-dependent transcription through the zinc finger protein Gis1. EMBO J *19*, 2569-2579.
Pu, M., Ni, Z., Wang, M., Wang, X., Wood, J.G., Helfand, S.L., Yu, H., and Lee, S.S. (2015). Trimethylation of Lys36 on H3 restricts gene expression change during aging and impacts life span. Genes Dev *29*, 718-731.
Rai, T.S., Cole, J.J., Nelson, D.M., Dikovskaya, D., Faller, W.J., Vizioli, M.G., Hewitt, R.N., Anannya, O., McBryan, T., Manoharan, I.*, et al.* (2014). HIRA orchestrates a dynamic chromatin landscape in senescence and is required for suppression of neoplasia. Genes Dev *28*, 2712-2725.
Riedel, C.G., Dowen, R.H., Lourenco, G.F., Kirienko, N.V., Heimbucher, T., West, J.A., Bowman, S.K., Kingston, R.E., Dillin, A., Asara, J.M.*, et al.* (2013). DAF-16 employs the chromatin remodeller SWI/SNF to promote stress resistance and longevity. Nat Cell Biol *15*, 491-501.

Rogina, B., Helfand, S.L., and Frankel, S. (2002). Longevity regulation by Drosophila Rpd3 deacetylase and caloric restriction. Science *298*, 1745.
Rohde, J.R., and Cardenas, M.E. (2003). The tor pathway regulates gene expression by linking nutrient sensing to histone acetylation. Mol Cell Biol *23*, 629-635.
Sarg, B., Koutzamani, E., Helliger, W., Rundquist, I., and Lindner, H.H. (2002). Postsynthetic trimethylation of histone H4 at lysine 20 in mammalian tissues is associated with aging. J Biol Chem *277*, 39195-39201.
Satoh, A., Brace, C.S., Rensing, N., Cliften, P., Wozniak, D.F., Herzog, E.D., Yamada, K.A., and Imai, S. (2013). Sirt1 extends life span and delays aging in mice through the regulation of Nk2 homeobox 1 in the DMH and LH. Cell Metab *18*, 416-430.
Schroeder, E.A., Raimundo, N., and Shadel, G.S. (2013). Epigenetic silencing mediates mitochondria stress-induced longevity. Cell Metab *17*, 954-964.
Sen, P., Dang, W., Donahue, G., Dai, J., Dorsey, J., Cao, X., Liu, W., Cao, K., Perry, R., Lee, J.Y.*, et al.* (2015). H3K36 methylation promotes longevity by enhancing transcriptional fidelity. Genes Dev *29*, 1362-1376.
Shah, P.P., Donahue, G., Otte, G.L., Capell, B.C., Nelson, D.M., Cao, K., Aggarwala, V., Cruickshanks, H.A., Rai, T.S., McBryan, T.*, et al.* (2013). Lamin B1 depletion in senescent cells triggers large-scale changes in gene expression and the chromatin landscape. Genes Dev *27*, 1787-1799.
Shimi, T., Butin-Israeli, V., Adam, S.A., Hamanaka, R.B., Goldman, A.E., Lucas, C.A., Shumaker, D.K., Kosak, S.T., Chandel, N.S., and Goldman, R.D. (2011). The role of nuclear lamin B1 in cell proliferation and senescence. Genes Dev *25*, 2579-2593.
Siebold, A.P., Banerjee, R., Tie, F., Kiss, D.L., Moskowitz, J., and Harte, P.J. (2010). Polycomb Repressive Complex 2 and Trithorax modulate Drosophila longevity and stress resistance. Proc Natl Acad Sci U S A *107*, 169-174.
Sun, D., Luo, M., Jeong, M., Rodriguez, B., Xia, Z., Hannah, R., Wang, H., Le, T., Faull, K.F., Chen, R.*, et al.* (2014). Epigenomic profiling of young and aged HSCs reveals concerted changes during aging that reinforce self-renewal. Cell Stem Cell *14*, 673-688.
Tissenbaum, H.A., and Guarente, L. (2001). Increased dosage of a sir-2 gene extends lifespan in Caenorhabditis elegans. Nature *410*, 227-230.
Wood, J.G., Rogina, B., Lavu, S., Howitz, K., Helfand, S.L., Tatar, M., and Sinclair, D. (2004). Sirtuin activators mimic caloric restriction and delay ageing in metazoans. Nature *430*, 686-689.
Wullschleger, S., Loewith, R., and Hall, M.N. (2006). TOR signaling in growth and metabolism. Cell *124*, 471-484.

Supplemental Table 2- Protocols for aging research		
Models	***Description***	***Link/Reference***
Yeast	Yeast cell sorting	(Smeal et al., 1996)
	Mother enrichment program	(Lindstrom and Gottschling, 2009)
	Microdissection for replicative lifespan assays	(Steffen et al., 2009)
	Chronological lifespan assays	(Fabrizio et al., 2001)
	High throughput analysis of replicative lifespans using a microfluidic system	(Jo et al., 2015; Liu et al., 2015; Zhang et al., 2012)
	High throughput chronological lifespan assays using a Bioscreen machine	(Murakami et al., 2008)
	ChIP-seq	(Sen et al., 2015)
	RNA-seq	(Hu et al., 2014)
	RNA-seq for detecting cryptic transcription	(Sen et al., 2015)
	Whole genome sequencing	(Hu et al., 2014)
	MNase seq	(Hu et al., 2014)
Worm	Worm lifespan measurement	Journal of Visualized Experiments, Science Education Database. Essentials of Developmental Biology. Invertebrate Lifespan Quantification, 2015
	ChIP-seq	http://www.wormbook.org/chapters/www_chromatinanalysis/chromatinanalysis.html
	RNA-seq	(Pu et al., 2015), (Sen et al., 2015)
	RNA-seq for detecting cryptic transcription	(Sen et al., 2015)
Fly	Fly lifespan measurement	Journal of Visualized Experiments, Science Education Database. Essentials of Developmental Biology. Invertebrate Lifespan Quantification, 2015
	ChIP-seq	http://www.modencode.org/
	RNA-seq	(Daines et al., 2011)
Killifish	ChIP-seq	(Harel et al., 2015)
	RNA-seq	
	CRISPR-mediated gene knockout	
Mouse models	ChIP-seq	(Visel et al., 2009)
	RNA-seq	http://www.mouseencode.org/
	CRISPR-mediated gene knockout	http://www.genome-engineering.org/crispr/
Cell cultures	ChIP-seq	(Shah et al., 2013)
	RNA-seq	(Rai et al., 2014)
	CRISPR-mediated gene knockout	http://www.genome-engineering.org/crispr/

References

Daines, B., Wang, H., Wang, L., Li, Y., Han, Y., Emmert, D., Gelbart, W., Wang, X., Li, W., Gibbs, R.*, et al.* (2011). The Drosophila melanogaster transcriptome by paired-end RNA sequencing. Genome Res *21*, 315-324.

Fabrizio, P., Pozza, F., Pletcher, S.D., Gendron, C.M., and Longo, V.D. (2001). Regulation of longevity and stress resistance by Sch9 in yeast. Science *292*, 288-290.

Harel, I., Benayoun, B.A., Machado, B., Singh, P.P., Hu, C.K., Pech, M.F., Valenzano, D.R., Zhang, E., Sharp, S.C., Artandi, S.E*., et al.* (2015). A platform for rapid exploration of aging and diseases in a naturally short-lived vertebrate. Cell *160*, 1013-1026.
Hu, Z., Chen, K., Xia, Z., Chavez, M., Pal, S., Seol, J.H., Chen, C.C., Li, W., and Tyler, J.K. (2014). Nucleosome loss leads to global transcriptional up-regulation and genomic instability during yeast aging. Genes Dev *28*, 396-408.
Jo, M.C., Liu, W., Gu, L., Dang, W., and Qin, L. (2015). High-throughput analysis of yeast replicative aging using a microfluidic system. Proc Natl Acad Sci U S A *112*, 9364-9369.
Lindstrom, D.L., and Gottschling, D.E. (2009). The mother enrichment program: a genetic system for facile replicative life span analysis in Saccharomyces cerevisiae. Genetics *183*, 413-422, 411SI-413SI.
Liu, P., Young, T.Z., and Acar, M. (2015). Yeast Replicator: A High-Throughput Multiplexed Microfluidics Platform for Automated Measurements of Single-Cell Aging. Cell Rep *13*, 634-644.
Murakami, C.J., Burtner, C.R., Kennedy, B.K., and Kaeberlein, M. (2008). A method for high-throughput quantitative analysis of yeast chronological life span. J Gerontol A Biol Sci Med Sci *63*, 113-121.
Pu, M., Ni, Z., Wang, M., Wang, X., Wood, J.G., Helfand, S.L., Yu, H., and Lee, S.S. (2015). Trimethylation of Lys36 on H3 restricts gene expression change during aging and impacts life span. Genes Dev *29*, 718-731.
Rai, T.S., Cole, J.J., Nelson, D.M., Dikovskaya, D., Faller, W.J., Vizioli, M.G., Hewitt, R.N., Anannya, O., McBryan, T., Manoharan, I*., et al.* (2014). HIRA orchestrates a dynamic chromatin landscape in senescence and is required for suppression of neoplasia. Genes Dev *28*, 2712-2725.
Sen, P., Dang, W., Donahue, G., Dai, J., Dorsey, J., Cao, X., Liu, W., Cao, K., Perry, R., Lee, J.Y*., et al.* (2015). H3K36 methylation promotes longevity by enhancing transcriptional fidelity. Genes Dev *29*, 1362-1376.
Shah, P.P., Donahue, G., Otte, G.L., Capell, B.C., Nelson, D.M., Cao, K., Aggarwala, V., Cruickshanks, H.A., Rai, T.S., McBryan, T*., et al.* (2013). Lamin B1 depletion in senescent cells triggers large-scale changes in gene expression and the chromatin landscape. Genes Dev *27*, 1787-1799.
Smeal, T., Claus, J., Kennedy, B., Cole, F., and Guarente, L. (1996). Loss of transcriptional silencing causes sterility in old mother cells of S. cerevisiae. Cell *84*, 633-642.
Steffen, K.K., Kennedy, B.K., and Kaeberlein, M. (2009). Measuring replicative life span in the budding yeast. J Vis Exp.
Visel, A., Blow, M.J., Li, Z., Zhang, T., Akiyama, J.A., Holt, A., Plajzer-Frick, I., Shoukry, M., Wright, C., Chen, F*., et al.* (2009). ChIP-seq accurately predicts tissue-specific activity of enhancers. Nature *457*, 854-858.
Zhang, Y., Luo, C., Zou, K., Xie, Z., Brandman, O., Ouyang, Q., and Li, H. (2012). Single cell analysis of yeast replicative aging using a new generation of microfluidic device. PLoS One *7*, e48275.