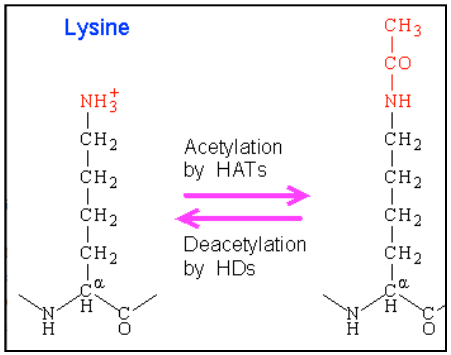
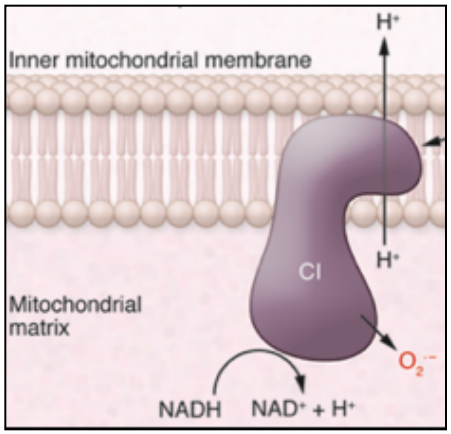
Cours du 27-10-2014

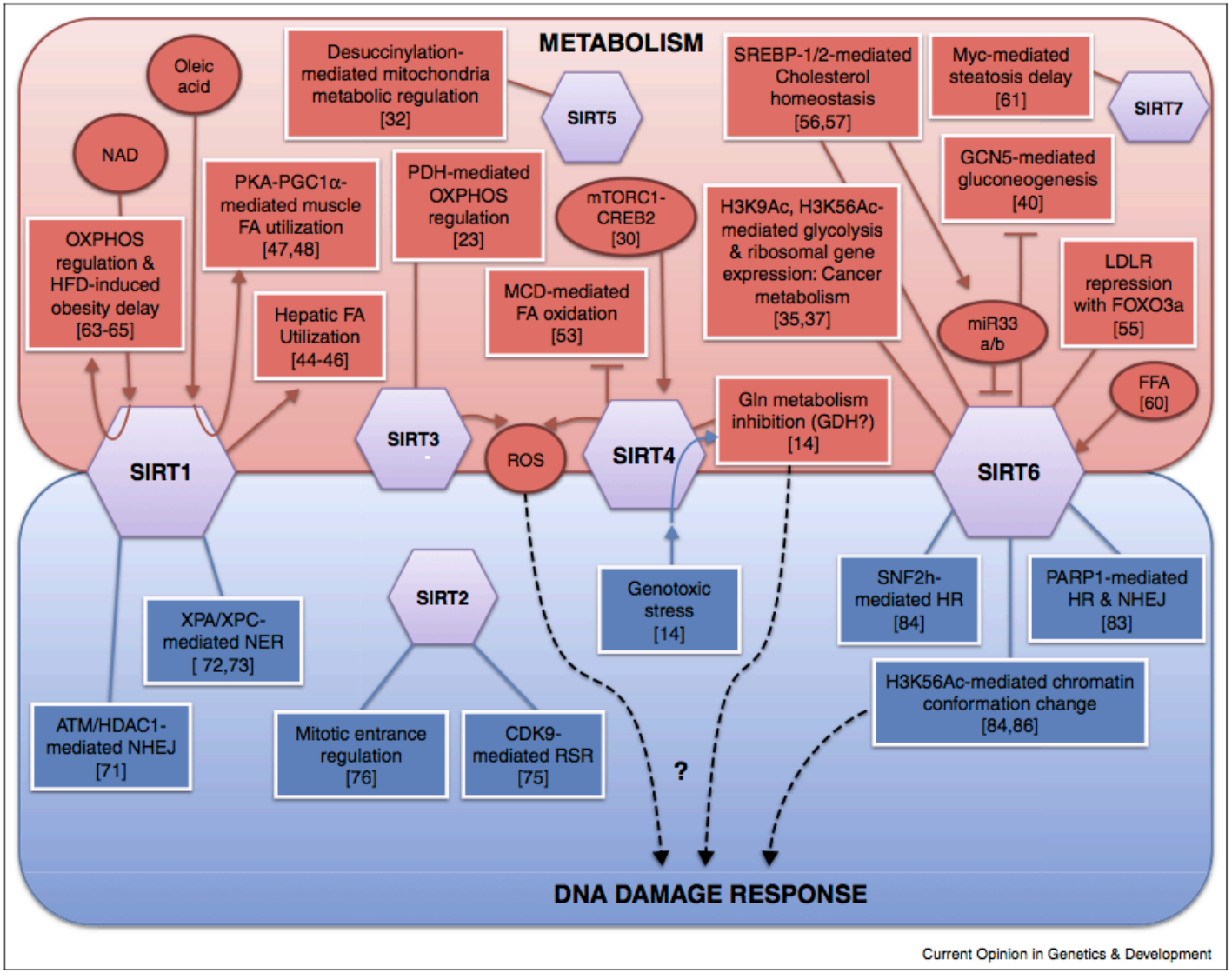
Sirtuins, metabolism, and DNA repair

Current Opinion in Genetics & Development
2014 vol. 26C pp. 24-32

Choi J, Mostoslavsky R







Sirtuins functions in metabolism and DNA repair. A diagram depicting the different functions for the mammalian sirtuins in cellular metabolism (red) and DNA repair (blue). Specific targets and biological roles are summarized.

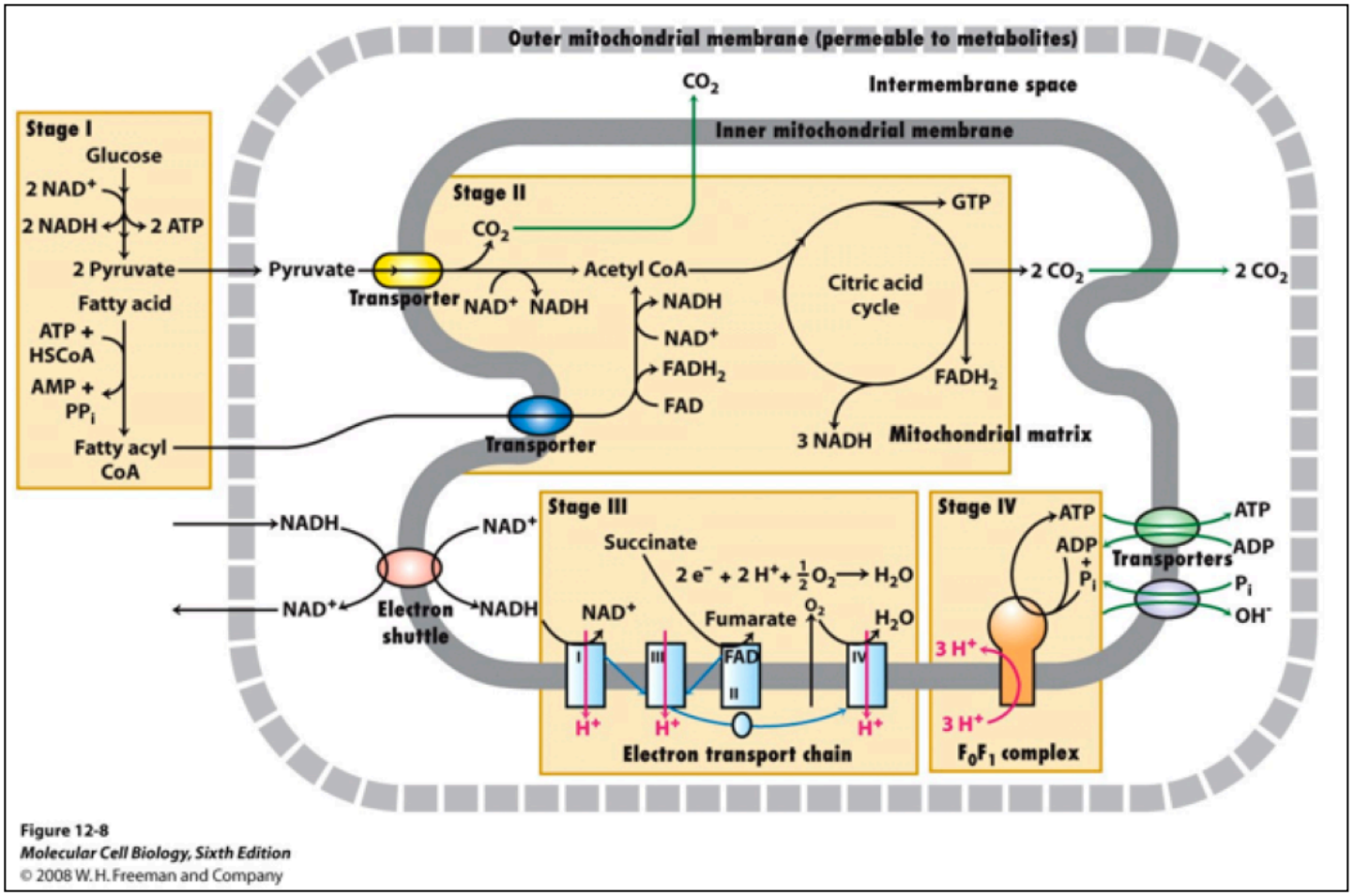
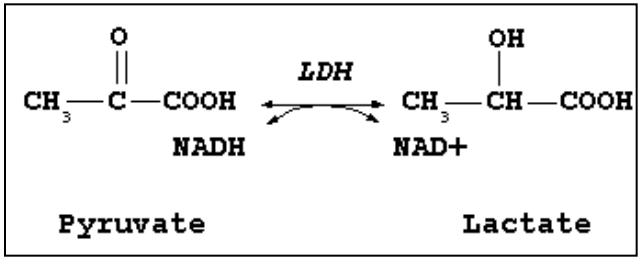
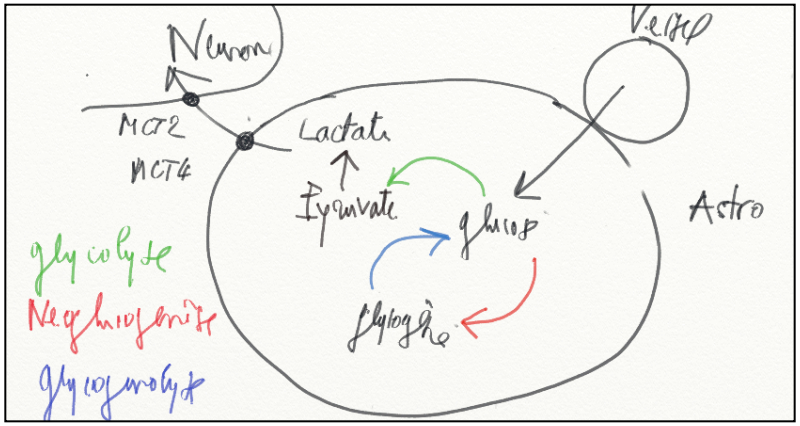


Figure 12-8
Molecular Cell Biology, Sixth Edition





Astrocyte-neuron lactate transport is required for long-term memory formation

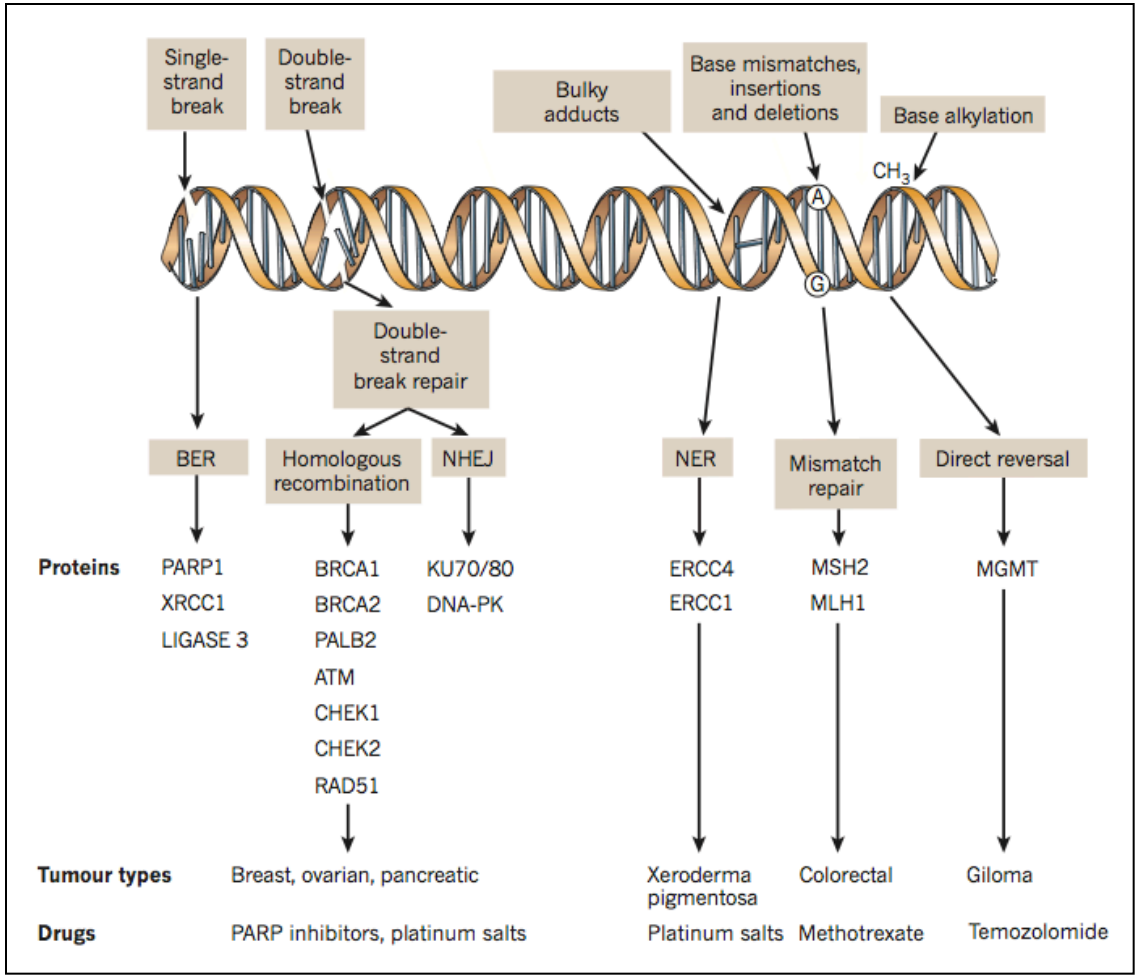
Suzuki A, Stern SA, Bozdagi O, Huntley GW, Walker RH, Magistretti PJ, Alberini CM

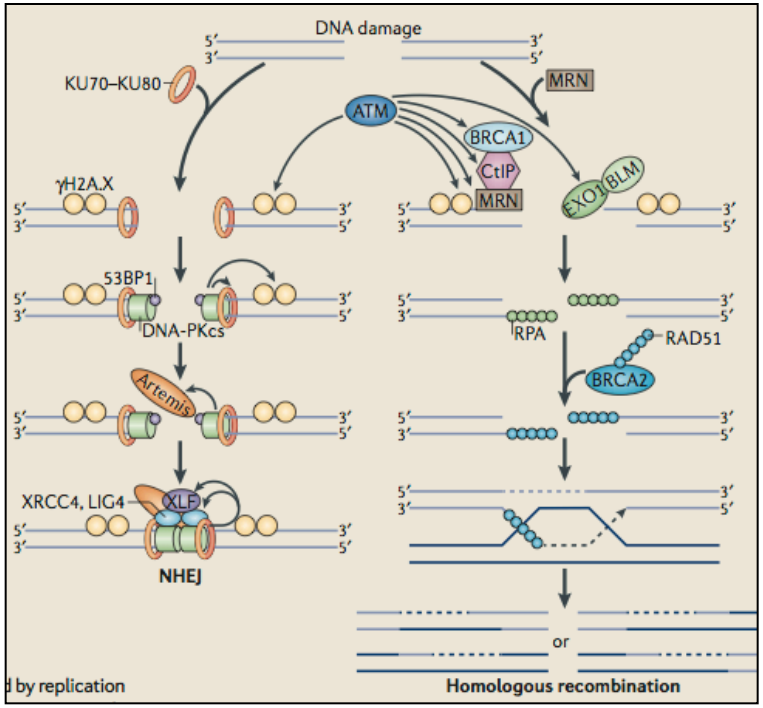
Cell
2011 vol. 144 (5) pp. 8...

The DNA damage response and cancer therapy

19 JANUARY 2012 | VOL 481 | NATURE | 287

Christopher J. Lord[1]* & Alan Ashworth[1]*





New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory?

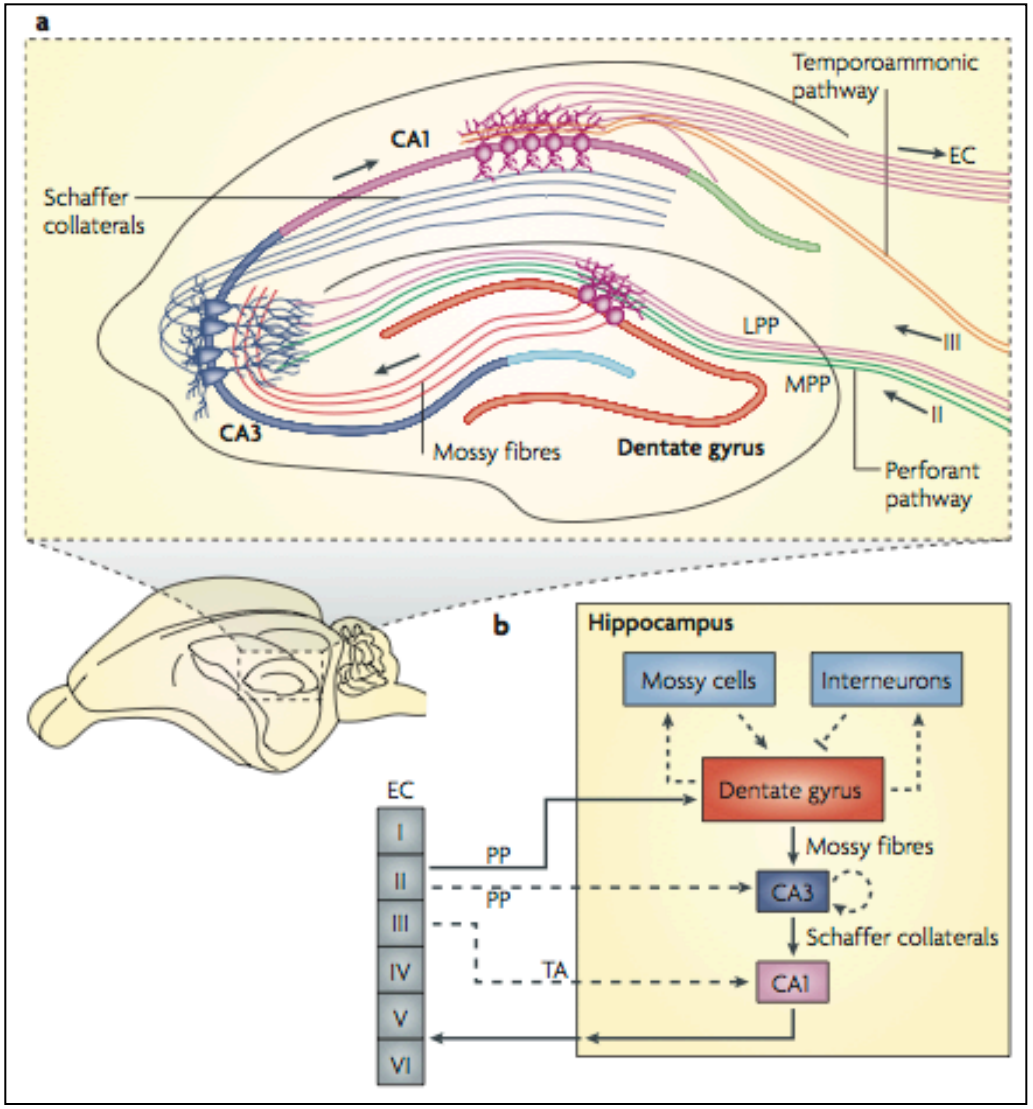
Deng W, Aimone J, Gage F

Nat Rev Neurosci
2010 vol. 11 (5) pp. 339–50

SIRT1 in Neurodevelopment and Brain Senescence

Herskovits AZ, Guarente L

Neuron
2014 vol. 81 (3) pp. 471–483



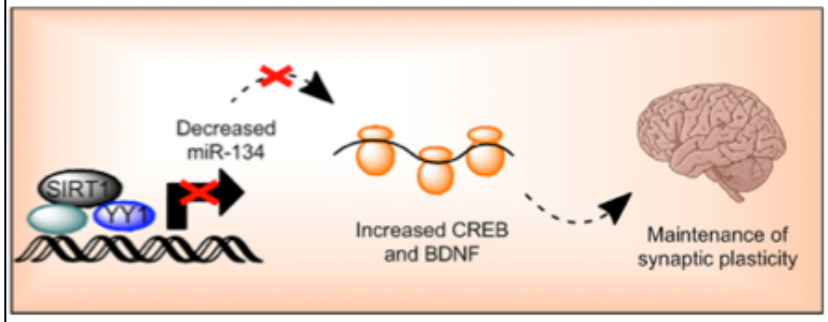
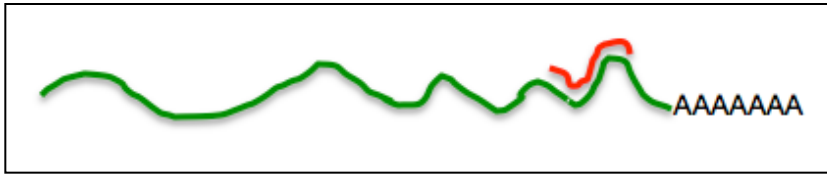


Figure 2. The Regulation of Learning and Memory by Sirtuin 1
In the hippocampus, SIRT1 affects synaptic plasticity via a repressor complex containing the transcription factor YY1, which regulates microRNA-134 (miR-134). This brain-specific microRNA regulates cAMP response binding protein (CREB) and brain-derived neurotrophic factor (BDNF) expression (Gao et al., 2010). These proteins are important for synapse formation and long-term potentiation. SIRT1 knockout mice have impaired hippocampal-dependent memory that is associated with decreased long-term potentiation in the CA1 region of the hippocampus (Gao et al., 2010; Michán et al., 2010).



SIRT1 in Neurodevelopment and Brain Senescence

Neuron
2014 vol. 81 (3) pp. 471-483

Herskovits AZ, Guarente L

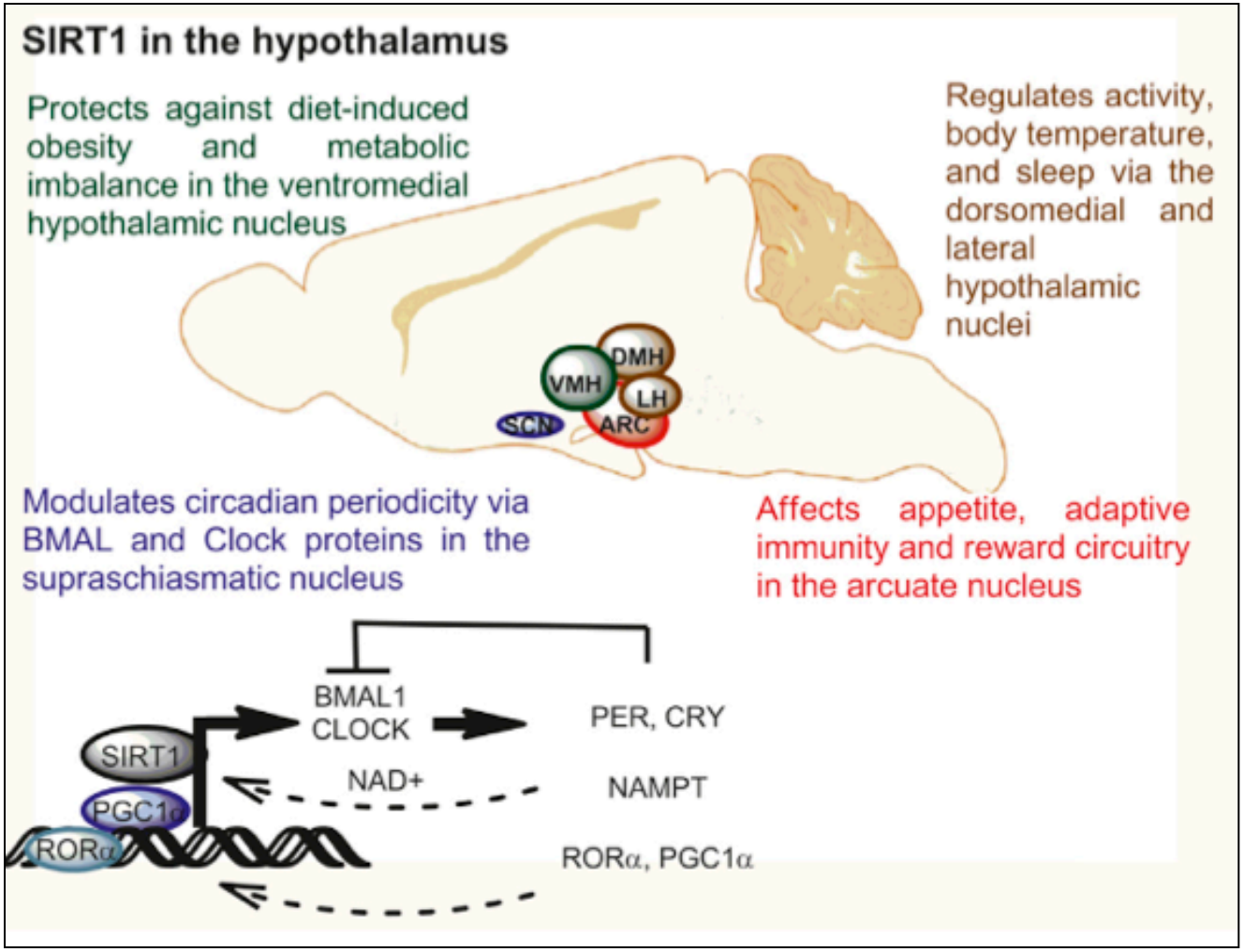


Figure 3. Sirtuin1 and Hypothalamic Function

The hypothalamus regulates physiology and behavior by coordinating neuroendocrine responses that modulate appetite, temperature, circadian control, and hormonal release to maintain homeostasis (Coppari, 2012). In the ventromedial hypothalamic nucleus, SIRT1 increases energy expenditure and protects against diet-induced obesity under fed high-fat diets (Ramadori et al., 2010, 2011). SIRT1 also regulates activity and body temperature in the dorsomedial and lateral hypothalamus (Satoh et al., 2010). In arcuate nucleus, SIRT1 modulates appetite and adaptive immunity (Dietrich et al., 2010; Matarese et al., 2013). In the supraschiasmatic nucleus of the hypothalamus, SIRT1 levels decrease with aging, affecting the activity pattern and circadian period. Overexpressing brain SIRT1 activates the transcription of BMAL and CLOCK proteins, enabling animals to be protected from aging-related changes to the central circadian clock (Chang and Guarente, 2013).

SIRT1 in Neurodevelopment and Brain Senescence

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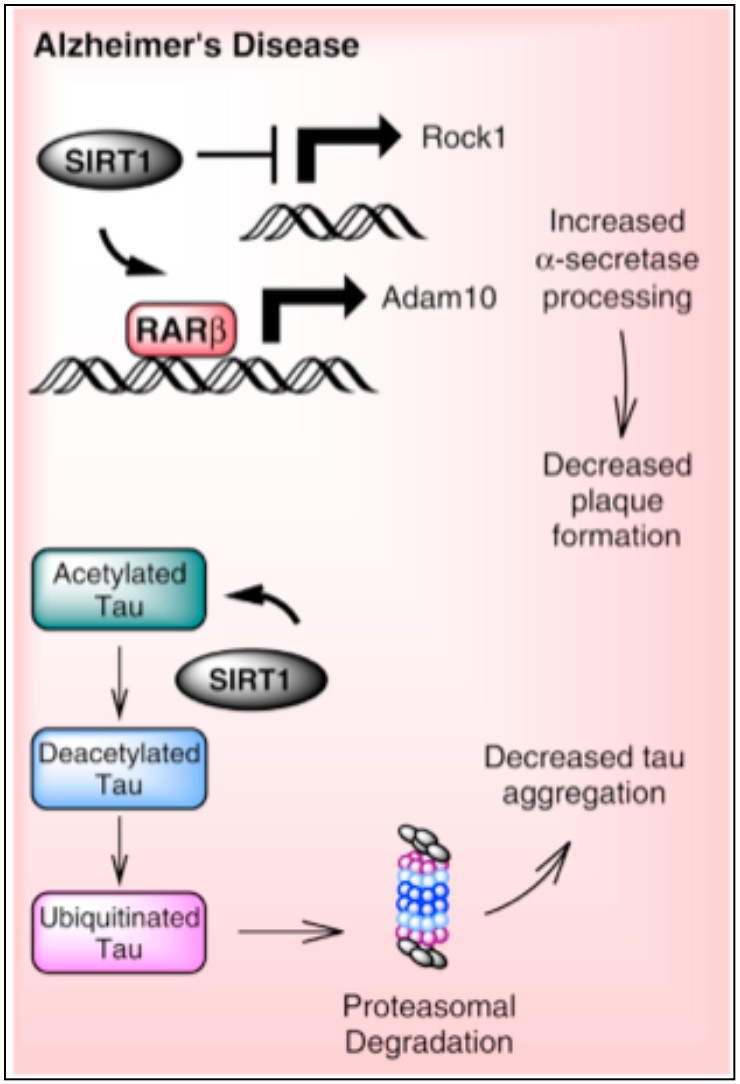
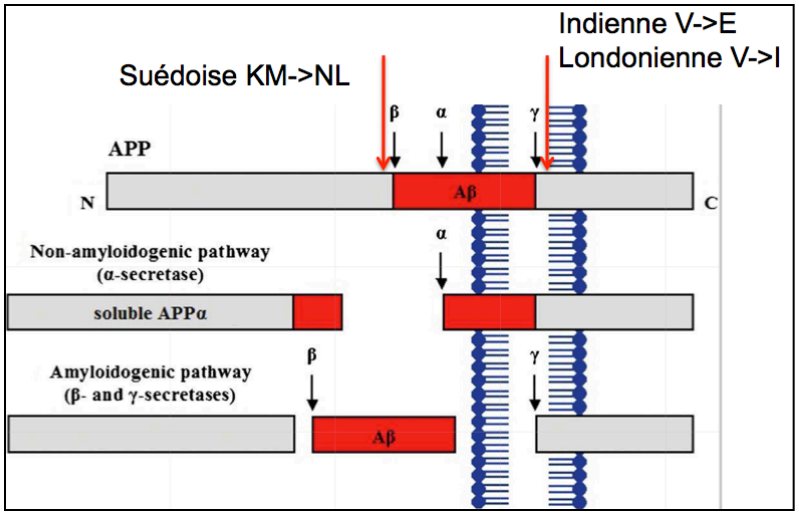
2014 vol. 81 (3) pp. 471-483

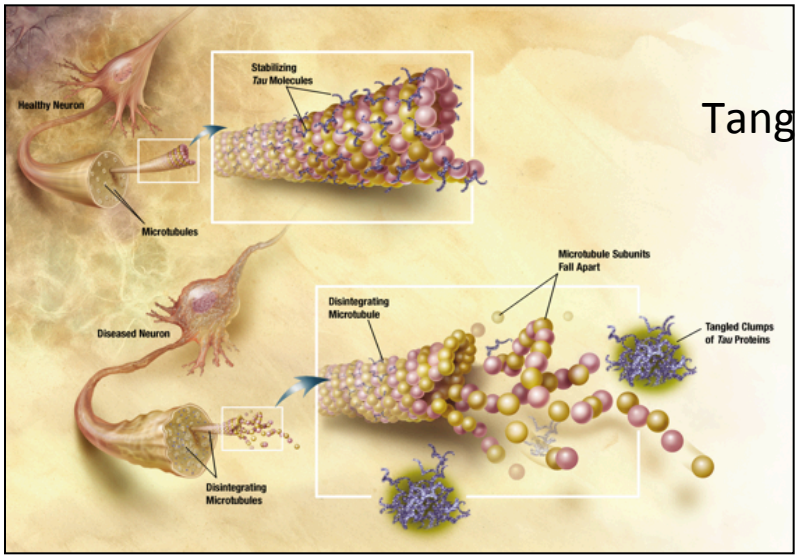
Clinics (Sao Paulo). 2011 June; 66(Suppl 1): 45–54.
doi: 10.1590/S1807-59322011001300006
PMCID: PMC3118437

Insights into Alzheimer disease pathogenesis from studies in transgenic animal models

Evelin L Schaeffer,[I] Micheli Figueiró,[I] and Wagner F Gattaz[I]





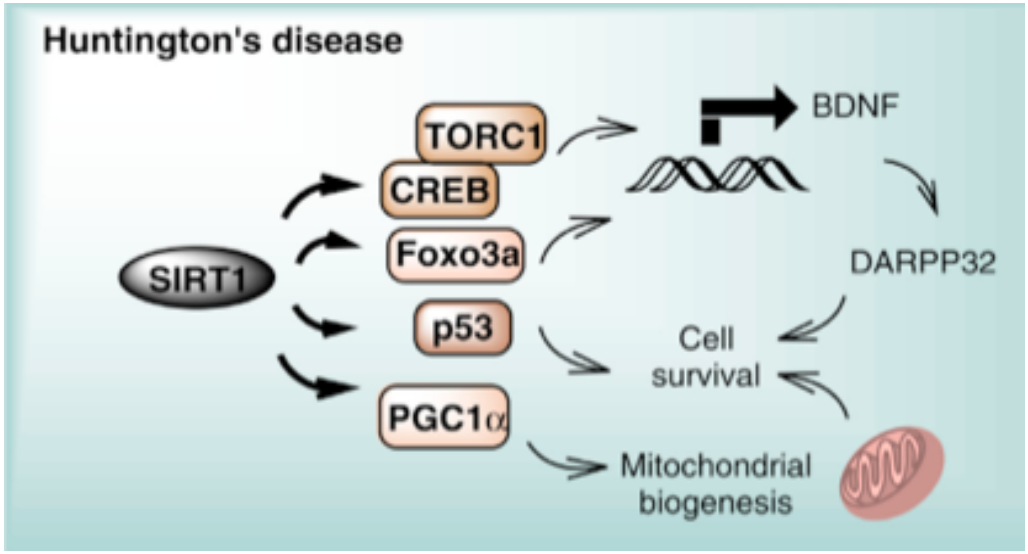


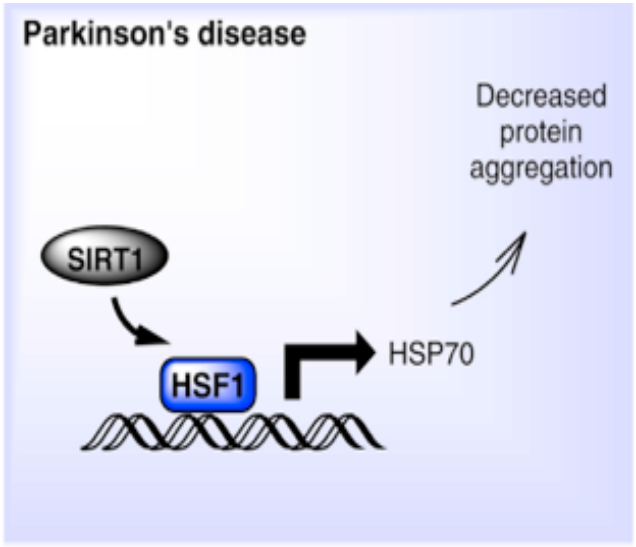
Tangles

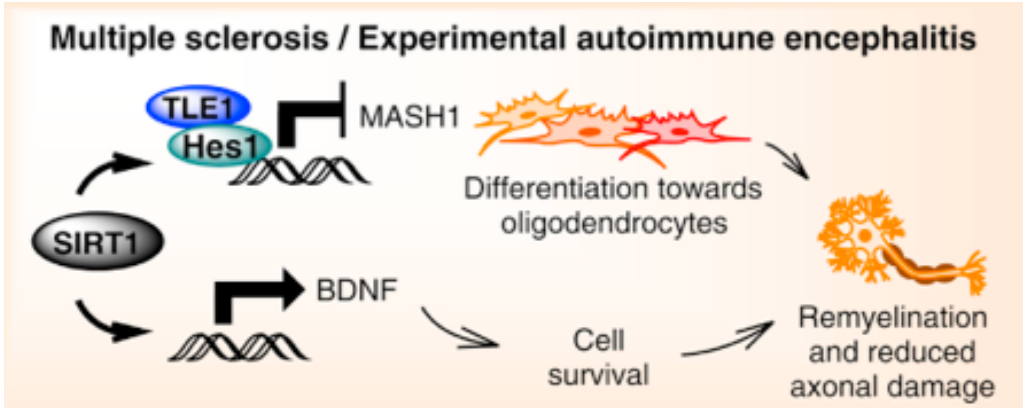
SIRT1 in Neurodevelopment and Brain Senescence

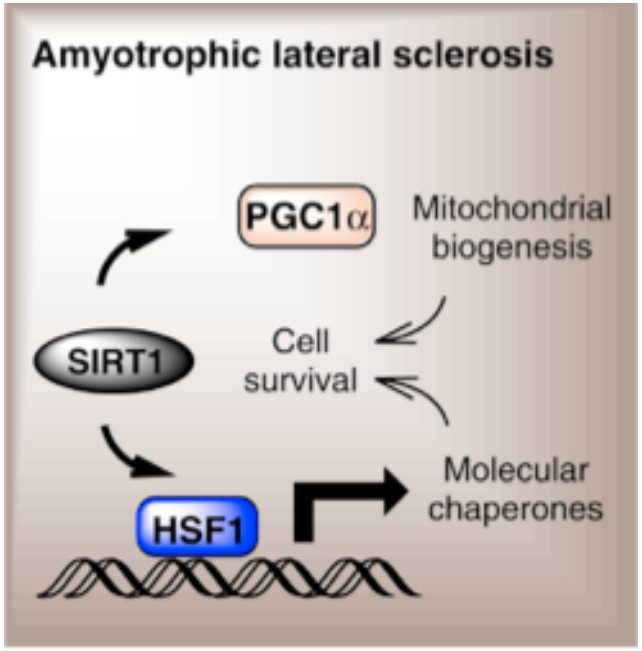
Herskovits AZ, Guarente L

Neuron
2014 vol. 81 (3) pp. 471-483









The SIRT1 Activator SRT1720 Extends Lifespan and Improves Health of Mice Fed a Standard Diet

Mitchell SJ, Martin-Montalvo A, Mercken EM, Palacios HH, Ward TM, Abulwerdi G, Minor RK, Vlasuk GP, Ellis JL, Sinclair DA, Dawson J, Allison DB, Zhang Y, Becker KG, Bernier M, de Cabo R

CELREP
2014 vol. 6 (5) pp. 836-43

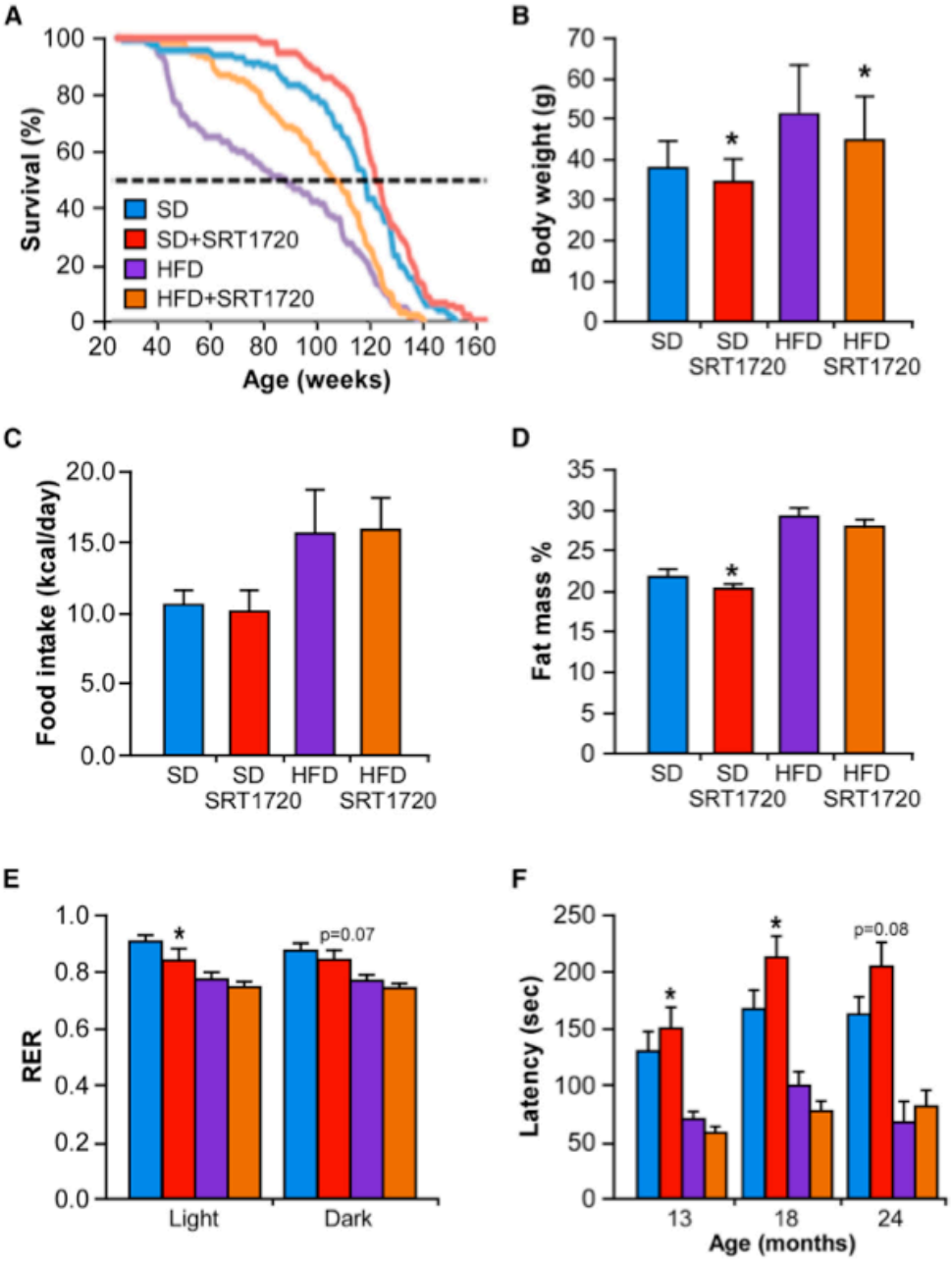


Figure 1. SRT1720 Extends Lifespan and Improves Health in Mice Fed a Standard Diet

(A) Kaplan-Meier survival curves for mice fed either a standard diet (SD) or high-fat diet (HFD) supplemented without or with SRT1720 (SD-SRT1720, HFD-SRT1720).

(B) Average body weight over the study.

(C) Average daily caloric intake over the study.

(D) Percentage fat mass measured by nuclear magnetic resonance spectroscopy at 13 months of age.

(E) Respiratory exchange ratio (RER).

(F) Rotarod performance.

Data are shown as mean ± SEM. *p $\leq$ 0.05 in comparison to diet without SRT1720.

The SIRT1 Activator SRT1720 Extends Lifespan and Improves Health of Mice Fed a Standard Diet

Mitchell SJ, Martin-Montalvo A, Mercken EM, Palacios HH, Ward TM, Abulwerdi G, Minor RK, Vlasuk GP, Ellis JL, Sinclair DA, Dawson J, Allison DB, Zhang Y, Becker KG, Bernier M, de Cabo R

CELREP
2014 vol. 6 (5) pp. 836-43

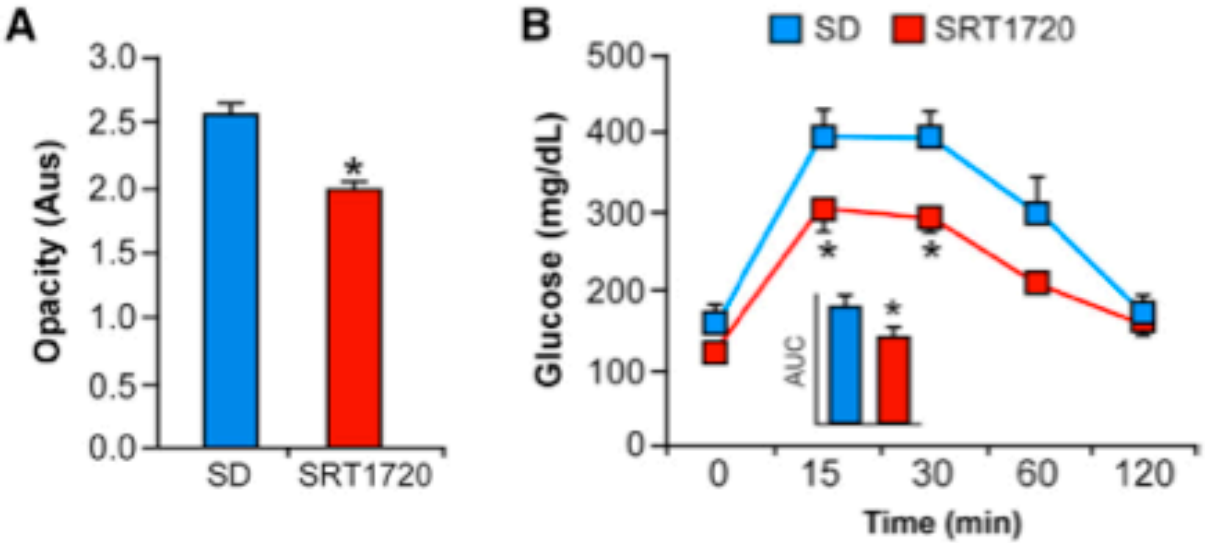
Figure 2. SRT1720 Improves the Quality of Life of SD-Fed Mice

(A) Cataract formation as assessed by lens opacity classification.

(B) Oral glucose tolerance test with area under the curve (inset).

(C) The homeostatic model assessment calculation of insulin resistance (HOMA-IR) and serum biochemical markers.

Data are shown as mean ± SEM. *$p \leq 0.05$ in comparison to SD diet without SRT1720.



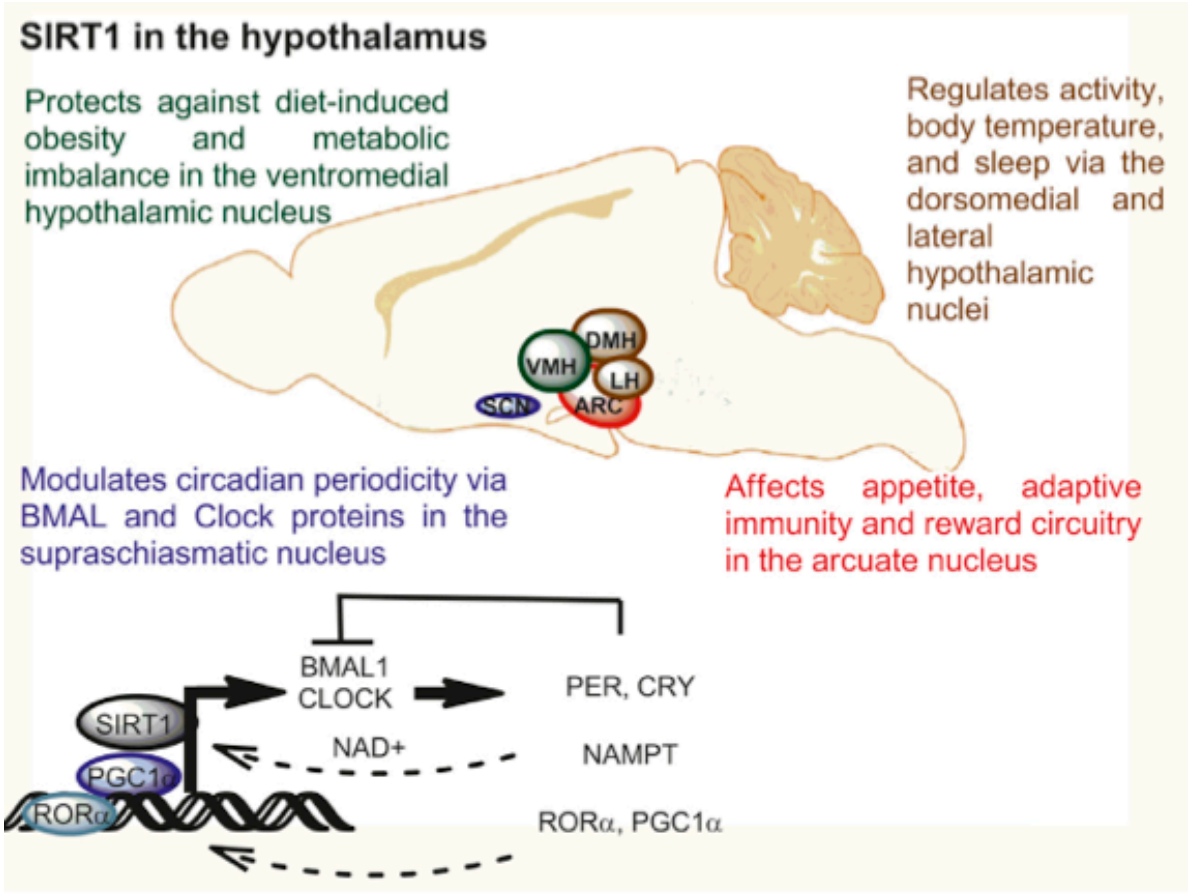
C

	SD	SRT1720
HOMA-IR (A.U.)	4.6 ± 0.1	2.4 ± 0.7
AST (U/L)	270 ± 35	190 ± 11*
CHOL (mg/dL)	221 ± 12	171 ± 7*
CK (U/L)	743 ± 152	367 ± 77*
Creatinine (mg/dL)	0.11 ± 0.01	0.14 ± 0.01*
LDL (mg/dL)	40 ± 5	24 ± 4*

SIRT1 in Neurodevelopment and Brain Senescence

Neuron
2014 vol. 81 (3) pp. 471-483

Herskovits AZ, Guarente L



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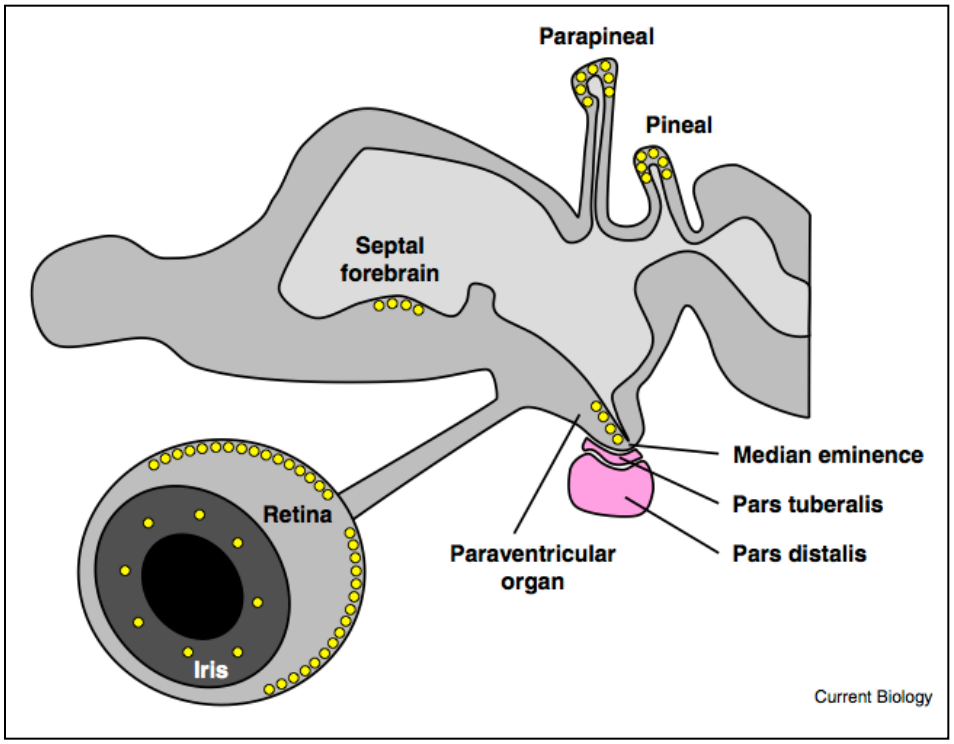
Neurobiology: The Eye within the Brain

Michael Menaker

Current Biology Vol 24 No 13
R614



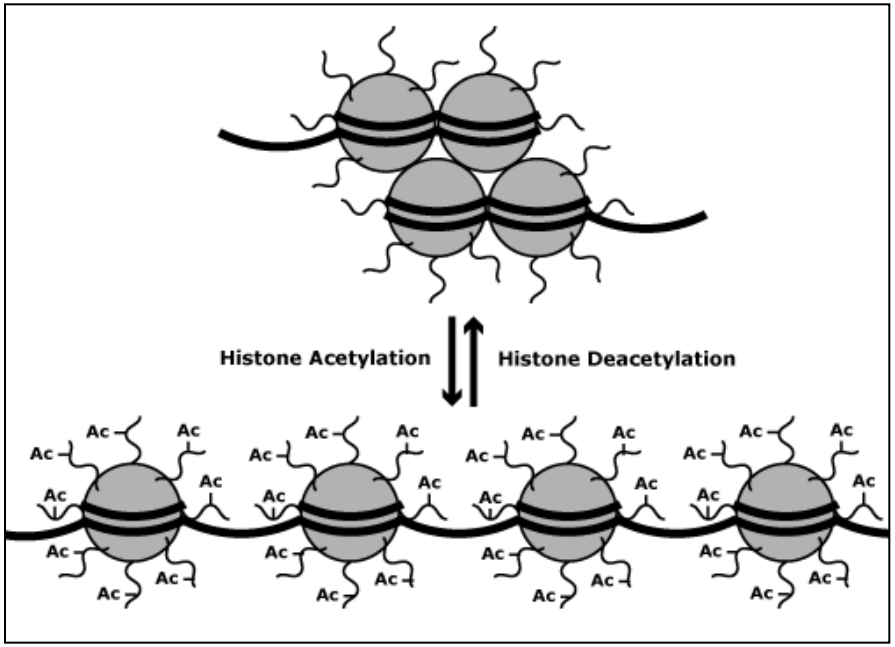


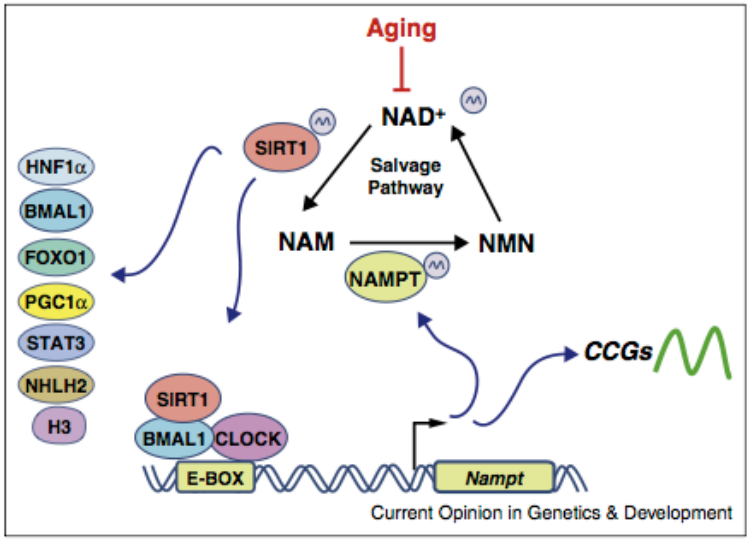
Figure 1. Non-visual photoreceptors in the vertebrate brain.

The parapineal and similar pineal-associated structures are only found in some fish, amphibians and reptiles, although the pineal itself is photoreceptive in all non-mammalian vertebrates. The iris is intrinsically photoreceptive in these groups as well and perhaps in some mammals. The putative locations of non-visual photoreceptors (shown in yellow) in the deep brain varies among the non-mammalian vertebrates. The adult mammalian pineal is not photoreceptive although it contains opsin. The only non-visual photoreceptors in mammals are intrinsically photosensitive ganglion cells in the retina. (Figure courtesy of I. Provencio.)

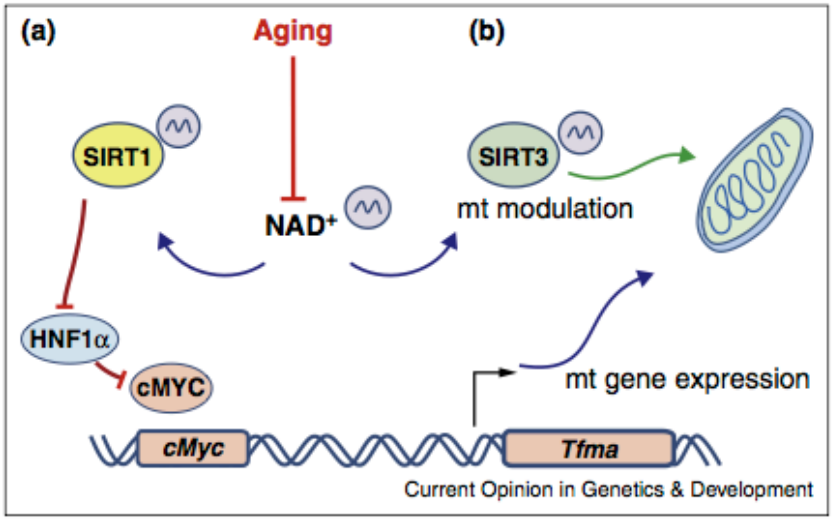
Circadian clock: linking epigenetics to aging

Orozco-Solis R, Sassone-Corsi P

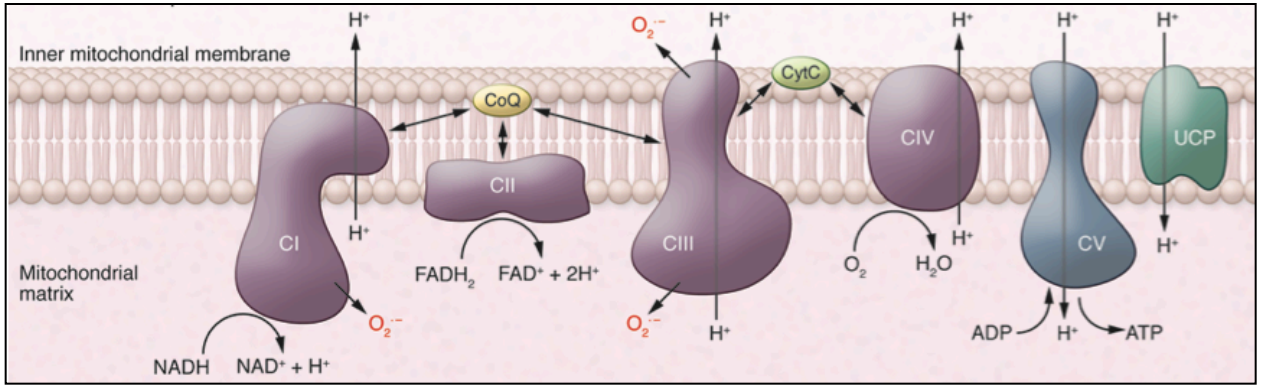
Current Opinion in Genetics & Development
2014 vol. 26C pp. 66-72

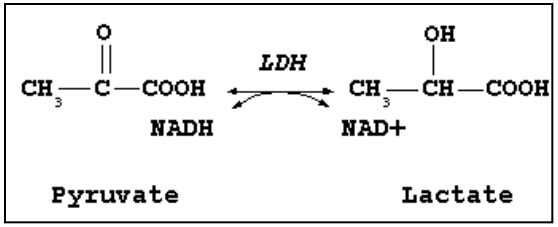


The NAD+ salvage pathway and its control by the circadian clock. The biosynthesis of NAD+ follows a circadian pattern, which is caused by the circadian expression of NAMPT, a rate-limiting enzyme in the NAD+ biosynthetic salvage pathway. The *Nampt* gene contains E-boxes in its promoter, leading to direct transcriptional control by the dimer CLOCK:BMAL1. The fluctuating levels of NAD+ modulate the activity of SIRT1 which in turn regulates the transcriptional activity of CLOCK:BMAL1 on their targets genes. During the aging the levels of NAD+ decreases and might alter the circadian rhythms of clock-controlled genes (CCGs)



Aging alters mitochondrial homeostasis. During aging the NAD+ synthesis decreases and consequently impairs the sirtuins activity, which have two consequences in the mitochondrial function: **(a)** The reduction of SIRT1 activity provokes the activation of HNF1α which in turn inhibits the transcription factor cMYC necessary to activate the transcription of *Tfam* which regulates the expression of mitochondrial genes. **(b)** Reduction of SIRT3 activity alters the function of mitochondrial proteins.





Circadian clock: linking epigenetics to aging

Current Opinion in Genetics & Development
2014 vol. 26C pp. 66–72

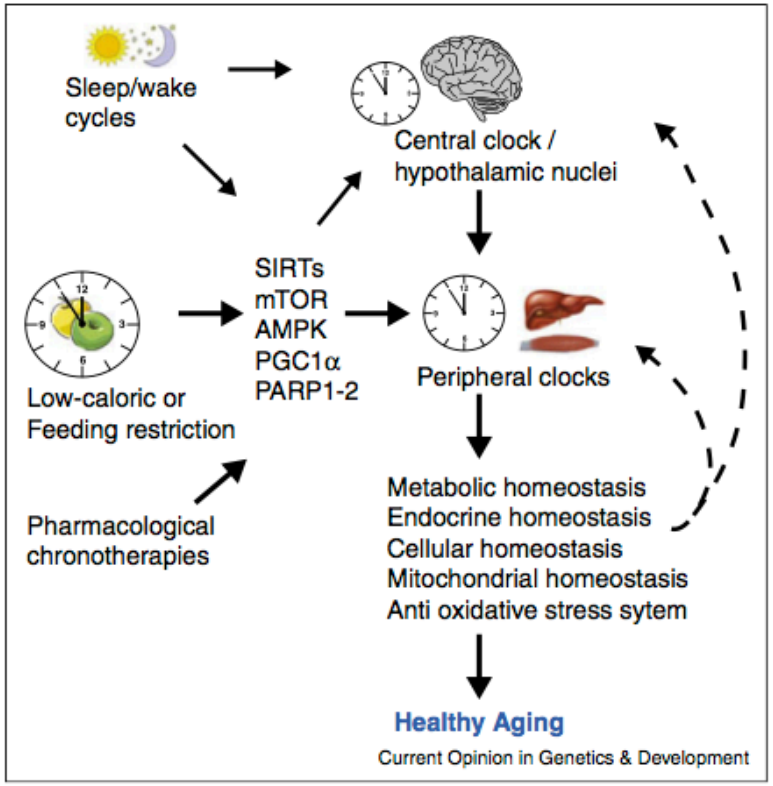
Orozco-Solis R, Sassone-Corsi P

Table 1

Nutrient sensors linking the clock system to the aging process

Protein	Circadian function	Aging phenotype	Reference
SIRT1	Regulates the circadian clock by BMAL1 and PER2 deacetylation. Activates BMAL1 and CLOCK in the SCN in young mice	Modulates mitochondrial function through NAD^+ levels in young mice	[7,8,33••,37••]
SIRT3	Modulates the circadian activity of the mitochondria by rhythms in the acetylation and activation of oxidative enzymes	In stems cells reverts the effect of aging-oxidative stress in mitochondria activating the anti-oxidative defense system	[40••,41•]
mTOR	Modulates rhythmically the translational control in circadian genes through 4E-BP1	Its inhibition extends lifespan in mice	[24,45•,49]
AMPK	Phosphorylates and destabilizes CRY1 altering the circadian rhythms in mice	Activated under low ATP levels, inhibits mTOR, and its pharmacological activation extend lifespan in mice	[52,55]

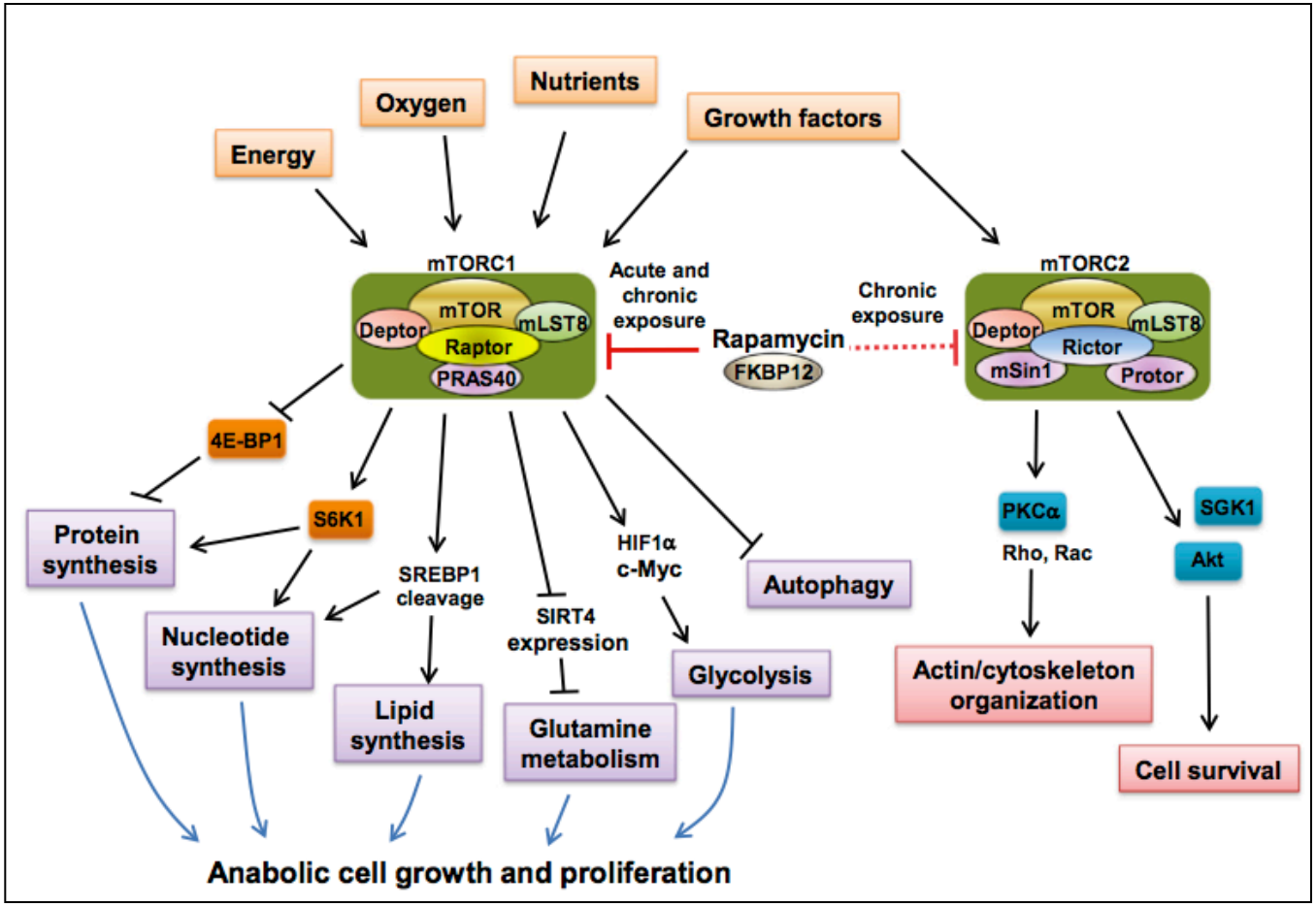
Nutrient sensors 'sense' the environmental conditions that modulate the circadian clock and the aging process. Healthy environment, such as enough sleeping time and low caloric diet/scheduled feeding, modulates nutrient sensors localized in the brain and peripheral tissues. These in turn synchronize the circadian clocks. As a consequence, the activation of anti-aging mechanisms improves the homeostasis at different levels promoting healthy aging. The different physiological conditions might decelerate or accelerate aging.



Rapamycin: One Drug, Many Effects

Cell Metabolism
2014 vol. 19 (3) pp. 373-379

Li J, Kim SG, Blenis J



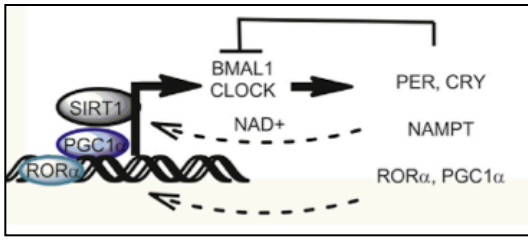


Figure 1. The Two mTOR Complexes and the Regulation of Key Cellular Processes

mTOR exists in two functionally distinct complexes, termed mTORC1 and mTORC2. mTORC1 integrates multiple signals from growth factors, oxygen, energy levels, and nutrients such as amino acids to promote cell growth and proliferation by activation of anabolic processes such as protein, lipid, and nucleotide synthesis; stimulation of energy metabolism such as glycolysis and glutaminolysis; and inhibition of catabolic process such as autophagy. Unlike mTORC1, mTORC2 only responds to growth factors and regulates actin/cytoskeleton organization and cell survival through the pathways as shown above. Rapamycin acutely inhibits mTORC1, whereas chronic exposure to rapamycin can also inhibit mTORC2.

SIRT1 in Neurodevelopment and Brain Senescence

Neuron
2014 vol. 81 (3) pp. 471-483

Herskovits AZ, Guarente L

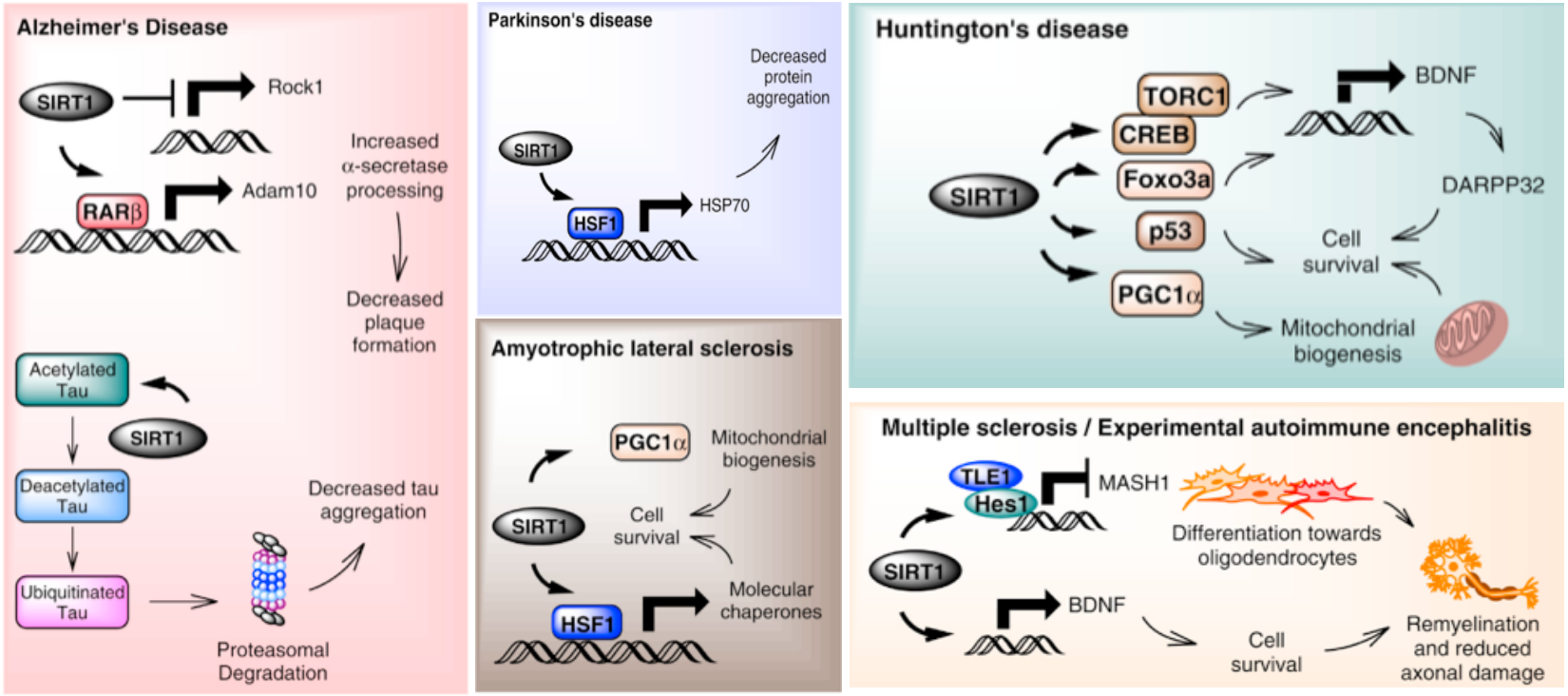


Figure 4. Major Targets and Mechanisms of SIRT1 in Mouse Models of Neurodegenerative Disease

Alzheimer's disease (highlighted in red). In Alzheimer's disease, SIRT1 has been shown to promote nonamyloidogenic APP-processing pathway by decreasing levels of ROCK1 kinase (Qin et al., 2006). SIRT1 also targets the retinoic acid receptor β, which activates ADAM10 to facilitate processing of APP along a nonamyloidogenic pathway (Donmez et al., 2010). SIRT1 has also been shown to directly deacetylate tau in several tauopathy models enabling ubiquitin ligases to promote clearance of this protein (Cohen et al., 2011; Min et al., 2010).

Parkinson's disease (highlighted in blue). SIRT1 has been shown to deacetylate HSF, which induces transcription of molecular chaperones that promote protein folding (Donmez et al., 2012; Raynes et al., 2012; Westerheide et al., 2009). In addition to its effects on the heat shock response, SIRT1 may also function to regulate autophagy and mitophagy, which may affect α-synuclein toxicity in the context of PD (Sampaio-Marques et al., 2012; Wu et al., 2011). There is also evidence that PGC1α may be a relevant target in mouse models of PD (Mudò et al., 2012).

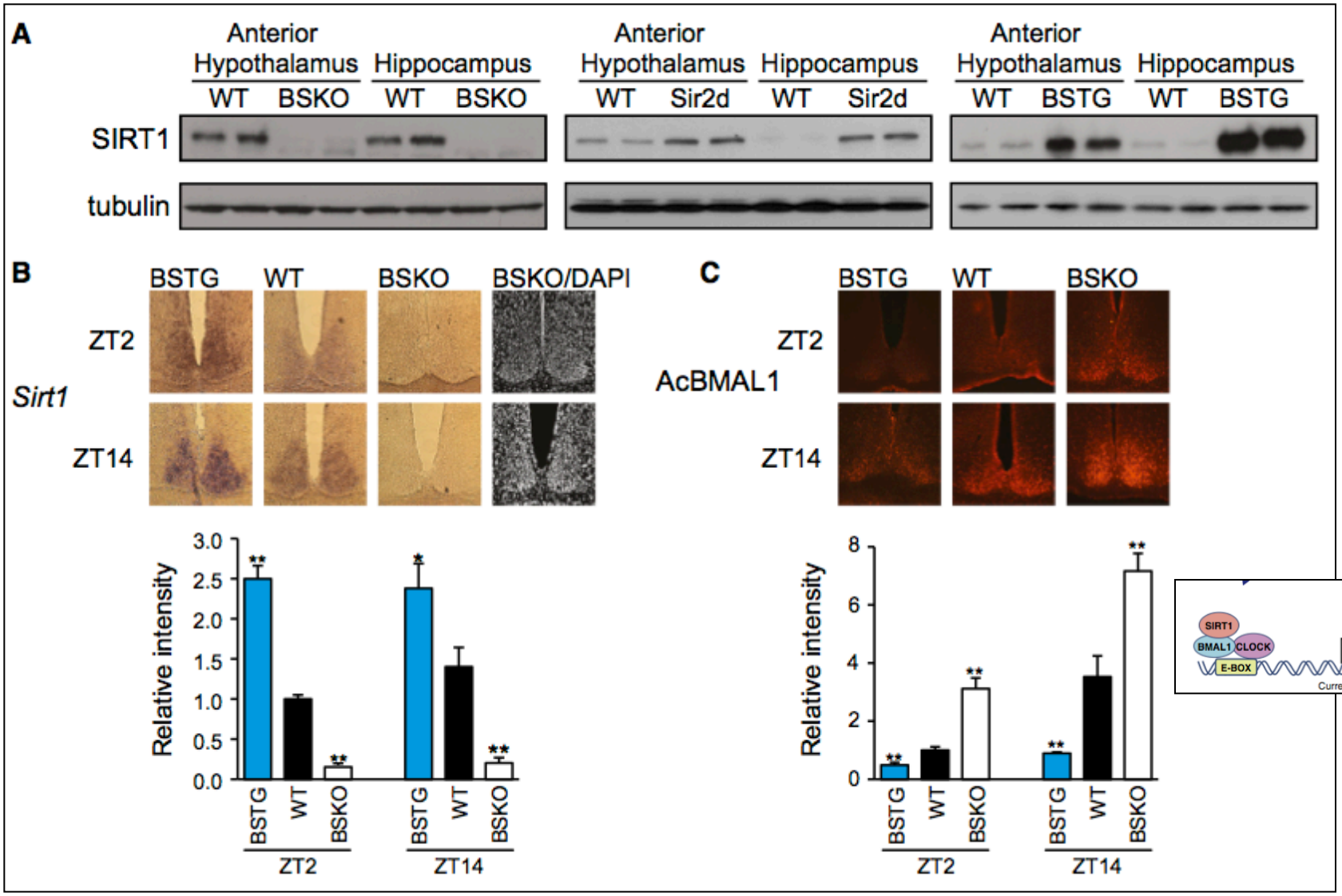
Huntington's disease (highlighted in green). Several different molecular mechanisms account for the protective effect of SIRT1 overexpression against mutant huntingtin toxicity (Jeong et al., 2012; Jiang et al., 2012). Mutant huntingtin protein was found to inhibit the enzymatic activity of SIRT1 during HD pathogenesis. One proposed mechanism is that SIRT1 deacetylates TORC1, facilitating BDNF transcription through CREB (Jeong et al., 2012). An alternate explanation for the protective effect of SIRT1 in HD mice was that this protein might maintain TrkB signaling and DARPP32 levels as HD progresses. Foxo3a deacetylation was another SIRT1 target implicated in promoting cell survival in the HD models (Jiang et al., 2012).

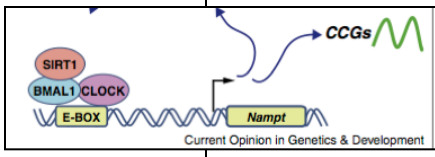
Amyotrophic lateral sclerosis (highlighted in beige). The proposed mechanism for SIRT1's activity in Amyotrophic lateral sclerosis parallels one of the pathways observed in PD. SIRT1 has been shown to deacetylate HSF1, which increases transcription of molecular chaperones including HSP70 and HSP25 that help to maintain intracellular protein homeostasis, reducing toxicity to motor neurons (Han et al., 2012; Raynes et al., 2012; van Ham et al., 2008; Westerheide et al., 2009). SIRT1 has also been shown to affect mitochondrial biogenesis in cell culture models of ALS and this may be due to deacetylation of PGC1α (Wang et al., 2011).

SIRT1 Mediates Central Circadian Control in the SCN by a Mechanism that Decays with Aging

CELL
2013 vol. 153 (7) pp. 1448-60

Chang H, Guarente L





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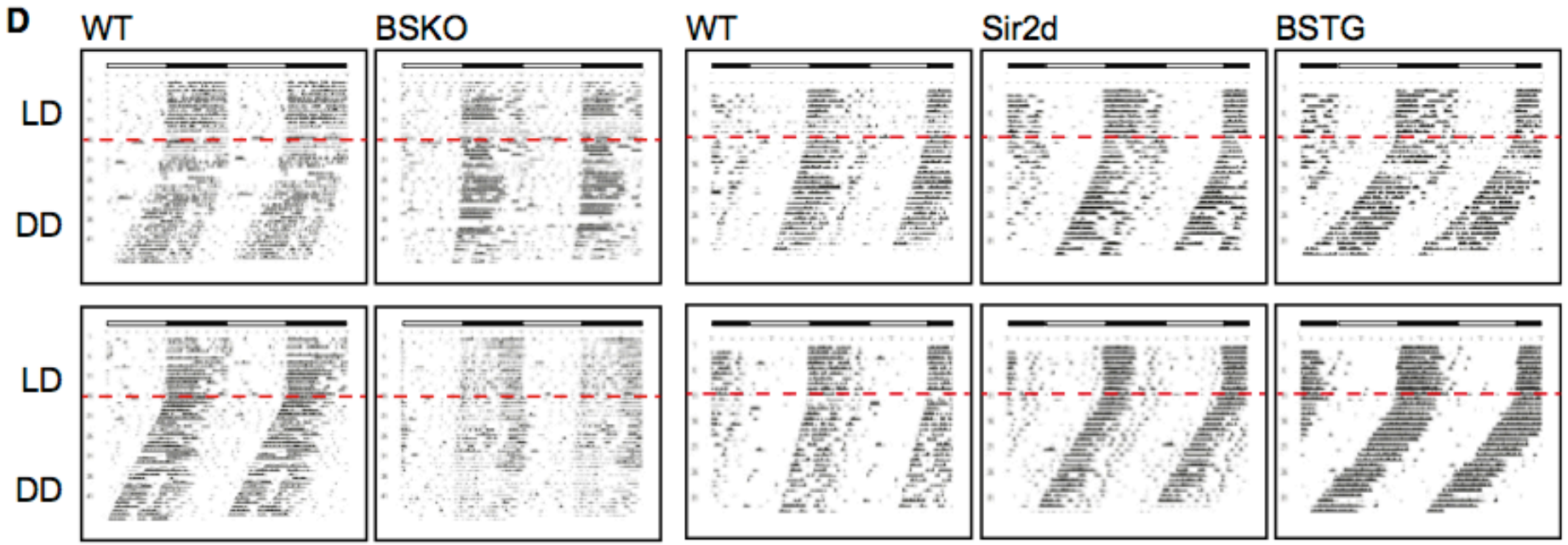
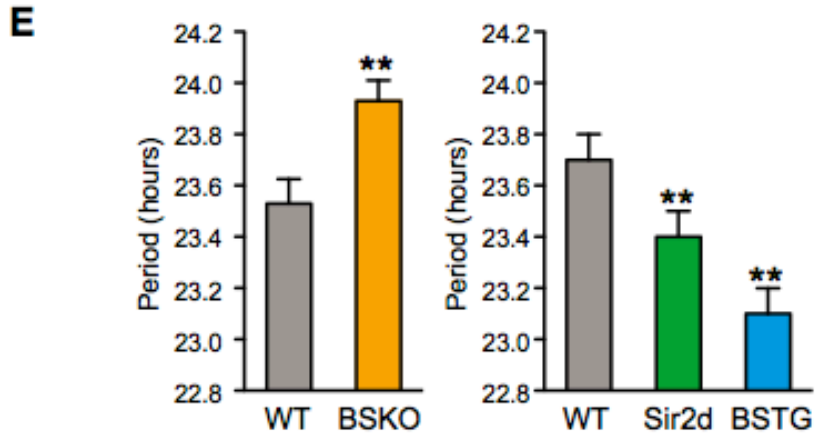
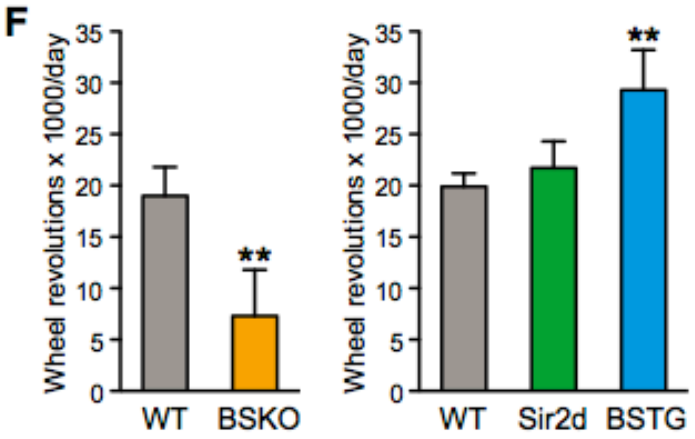
SIRT1 Mediates Central Circadian Control in the SCN by a Mechanism that Decays with Aging

CELL
2013 vol. 153 (7) pp. 1448-60







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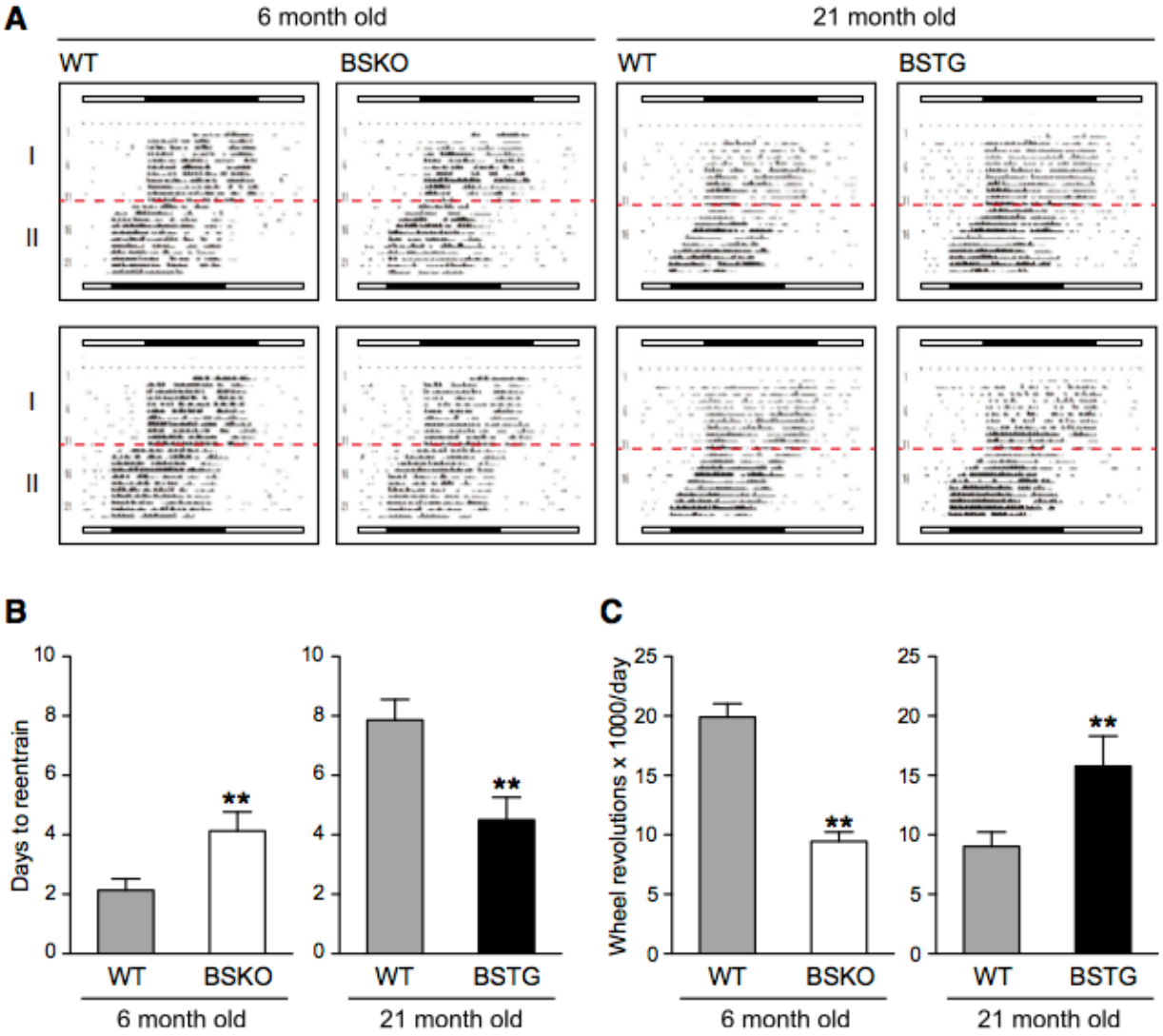
Chang H, Guarente L



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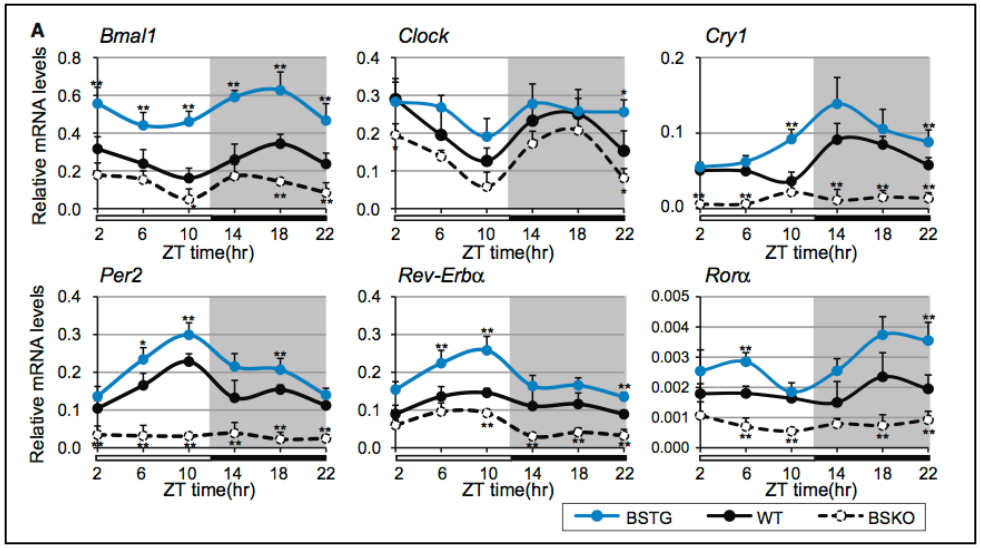
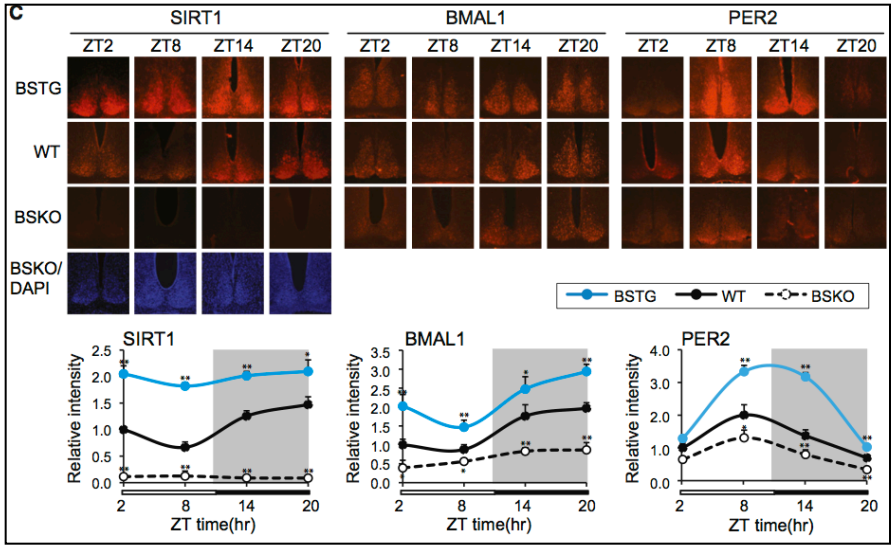
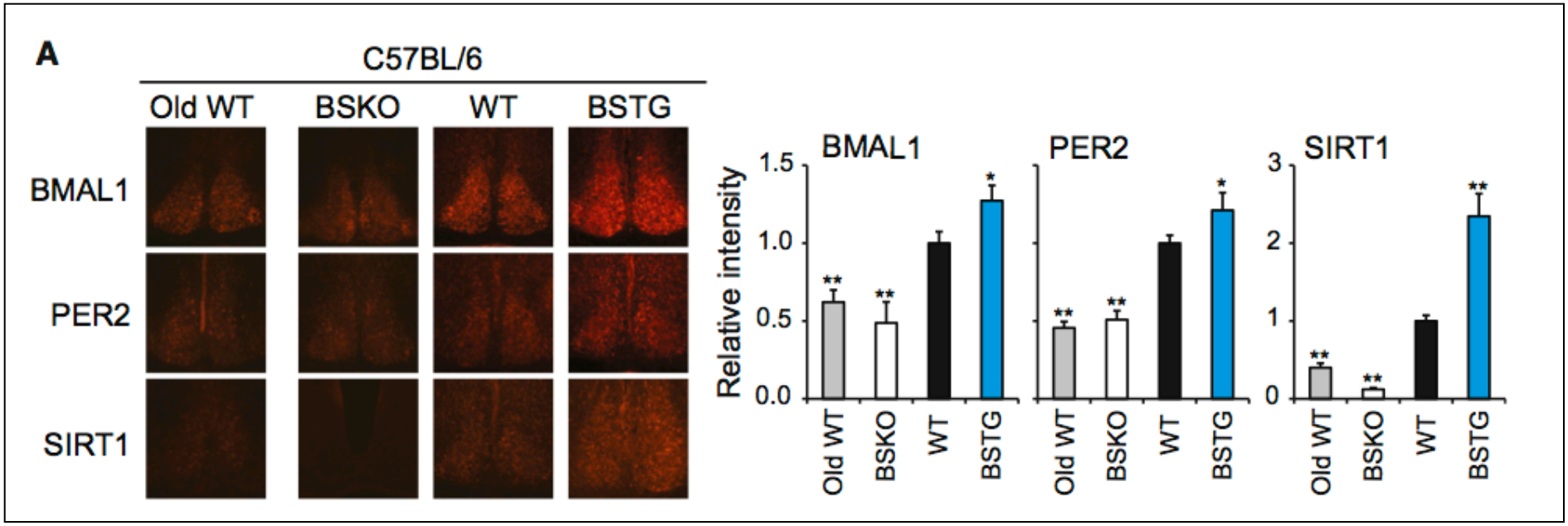
Chang H, Guarente L







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Chang H, Guarente L

CELL

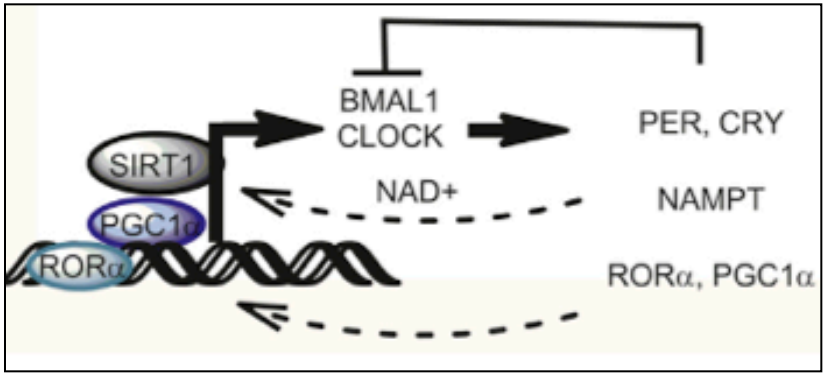
2013 vol. 153 (7) pp. 1448–60

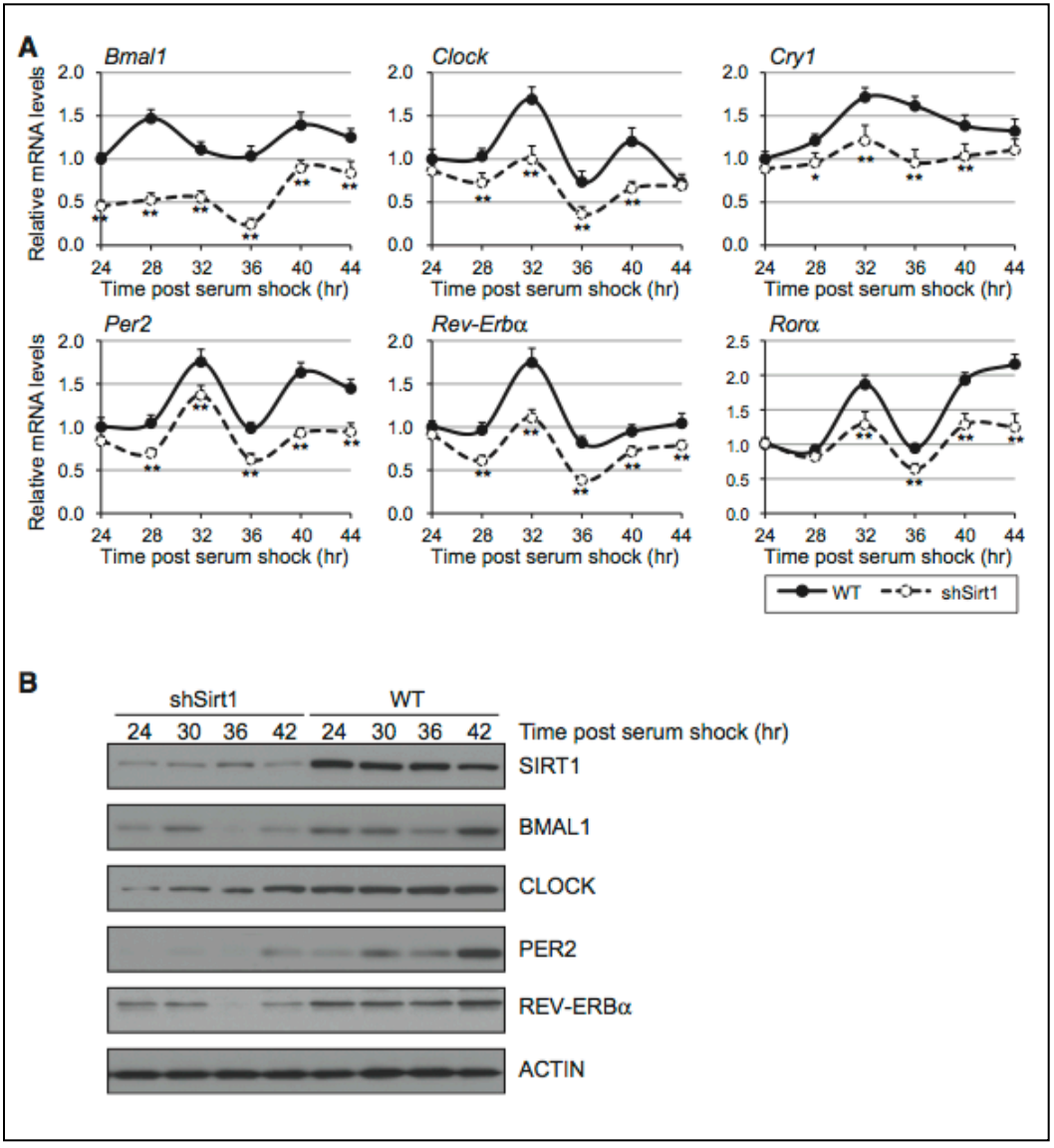
SIRT1 in Neurodevelopment and Brain Senescence

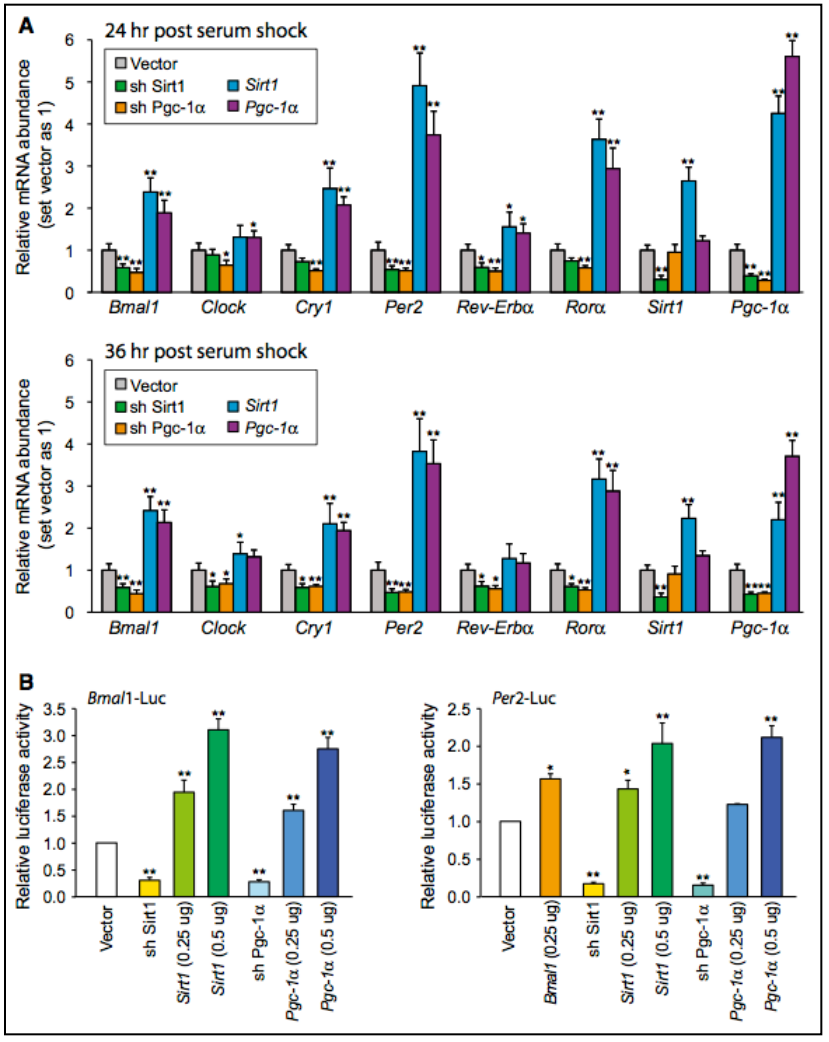
Herskovits AZ, Guarente L

Neuron

2014 vol. 81 (3) pp. 471–483







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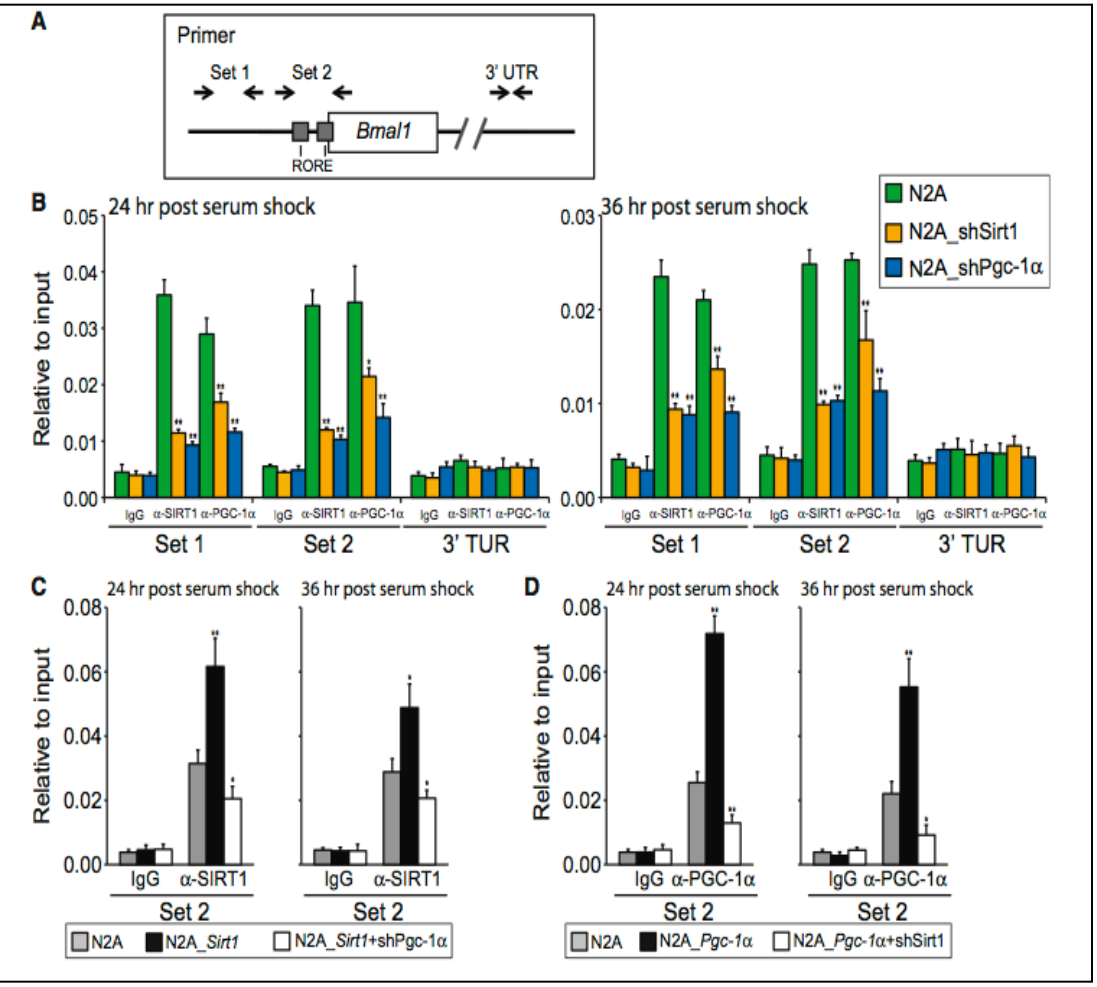
Chang H, Guarente L

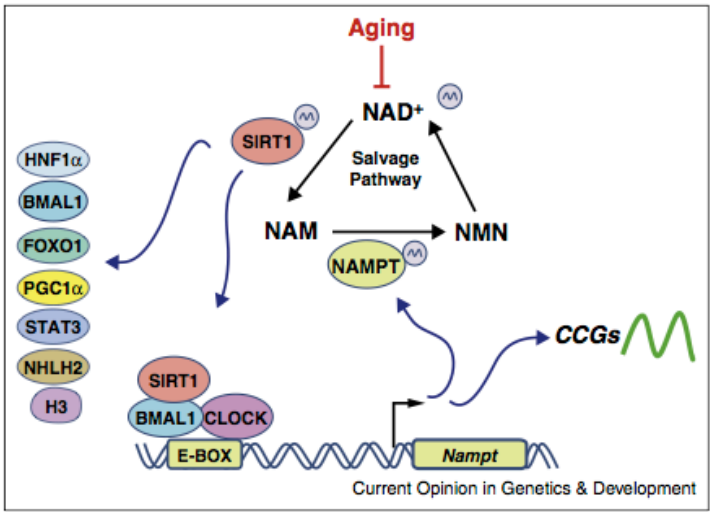
CELL
2013 vol. 153 (7) pp. 1448-60

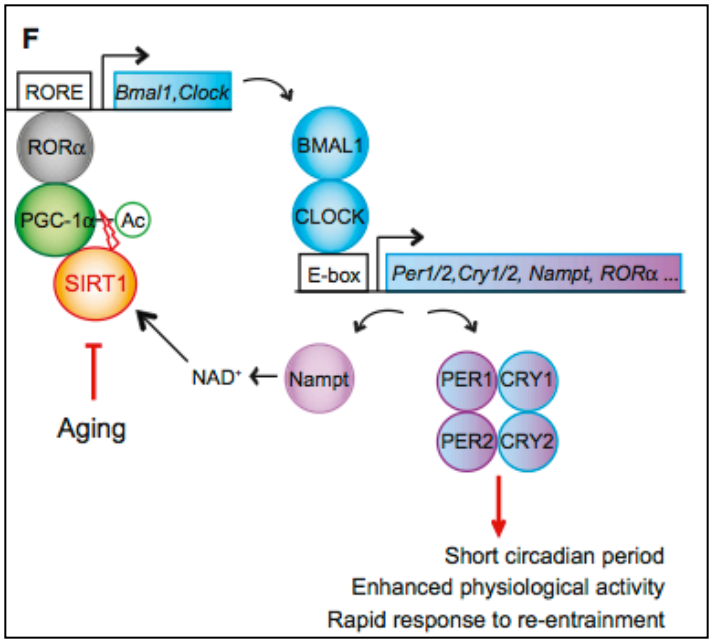
Circadian clock: linking epigenetics to aging

Orozco-Solis R, Sassone-Corsi P

Current Opinion in Genetics & Development
2014 vol. 26C pp. 66-72



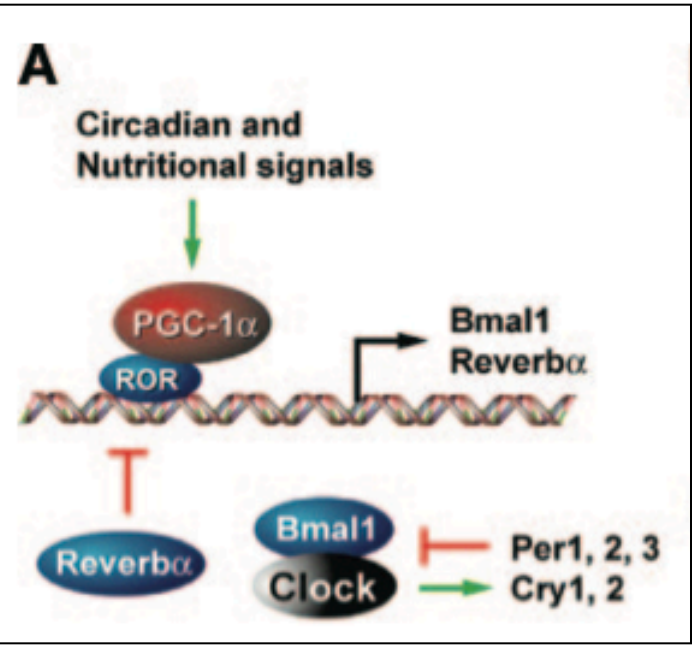


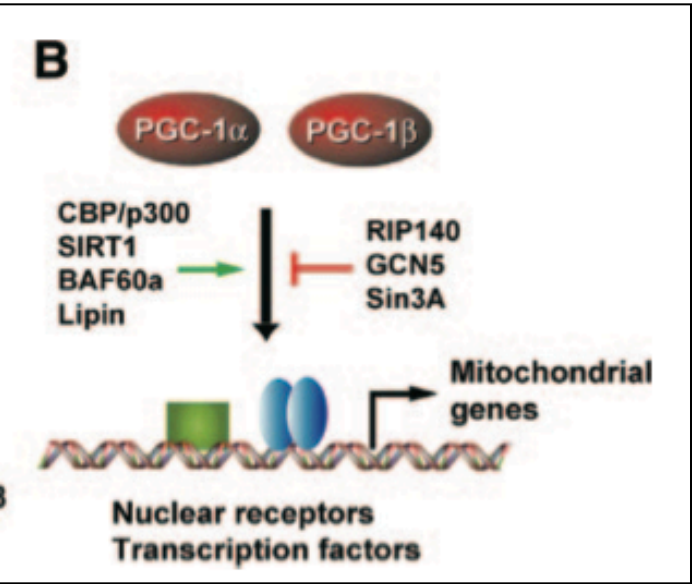


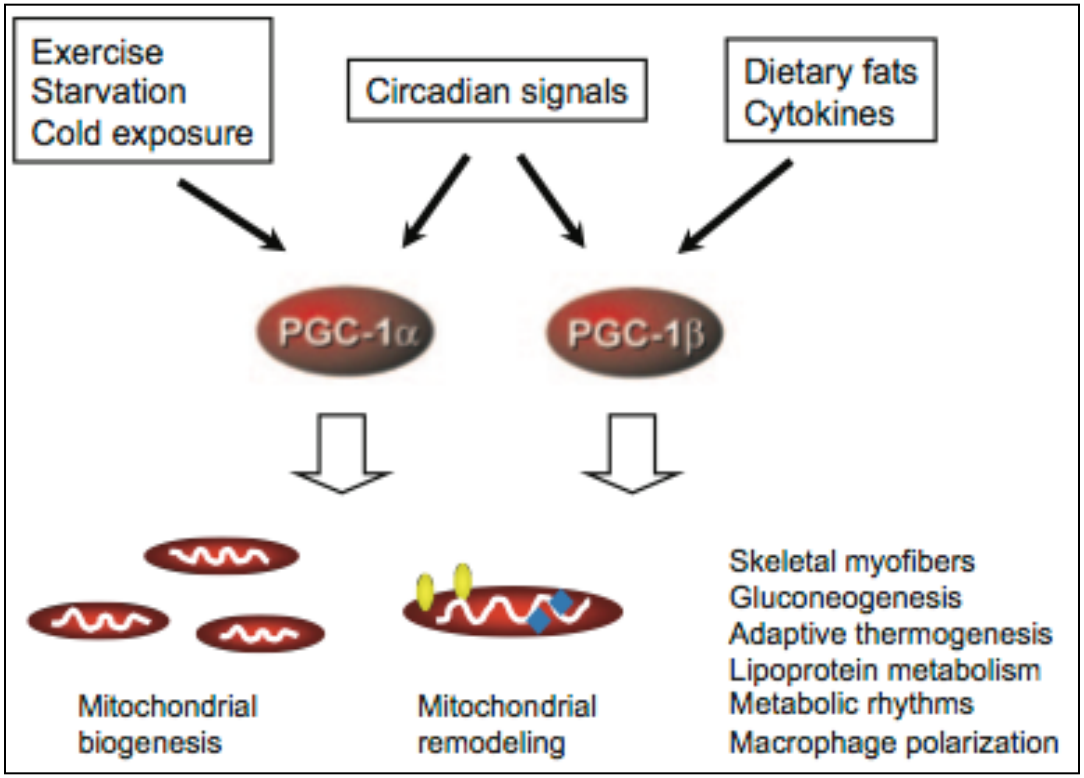
Minireview: The PGC-1 Coactivator Networks: Chromatin-Remodeling and Mitochondrial Energy Metabolism

Jiandie D. Lin

Mol Endocrinol, January 2009, 23(1):2–10



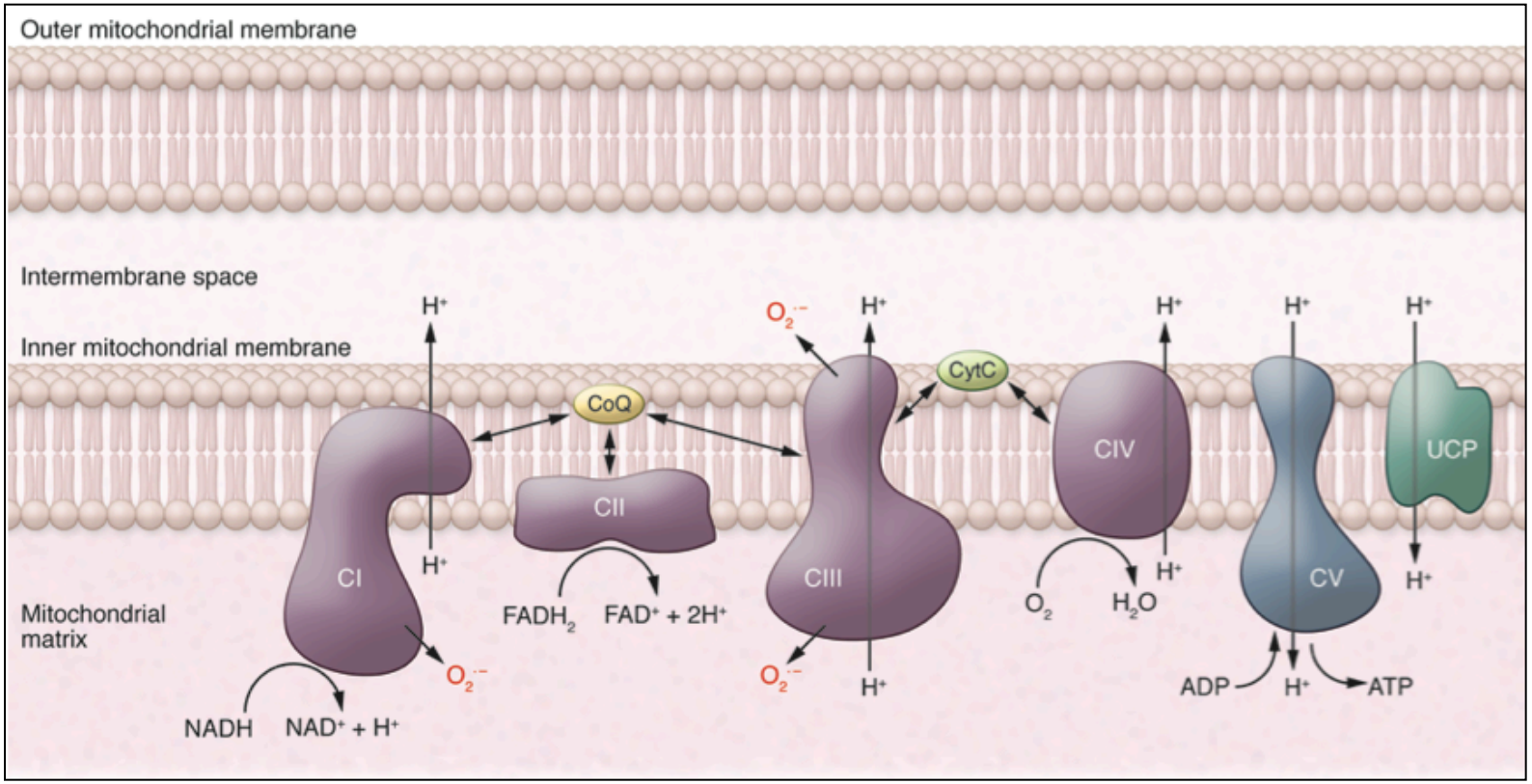


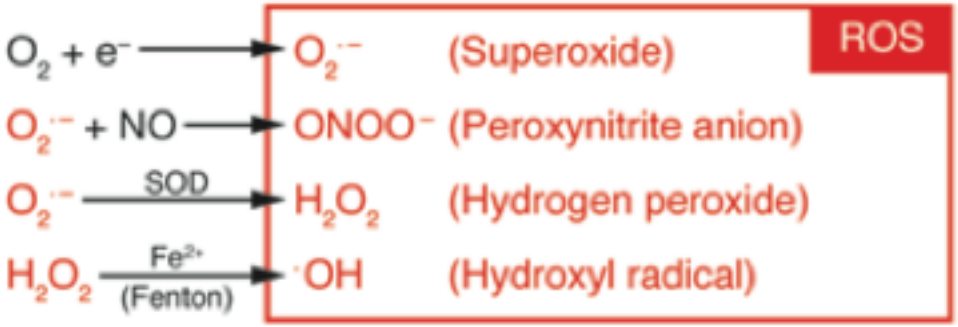


The role of mitochondria in aging

J Clin Invest
2013 vol. 123 (3) pp. 951–7

Bratic A, Larsson N





Suppression of Reactive Oxygen Species and Neurodegeneration by the PGC-1 Transcriptional Coactivators

Cell *127*, 397–408, October 20, 2006

Julie St-Pierre,[1,5,6] Stavit Drori,[1,5] Marc Uldry,[1] Jessica M. Silvaggi,[1] James Rhee,[1] Sibylle Jäger,[1] Christoph Handschin,[1] Kangni Zheng,[2] Jiandie Lin,[1,7] Wenli Yang,[1] David K. Simon,[2] Robert Bachoo,[3,4] and Bruce M. Spiegelman[1,*]

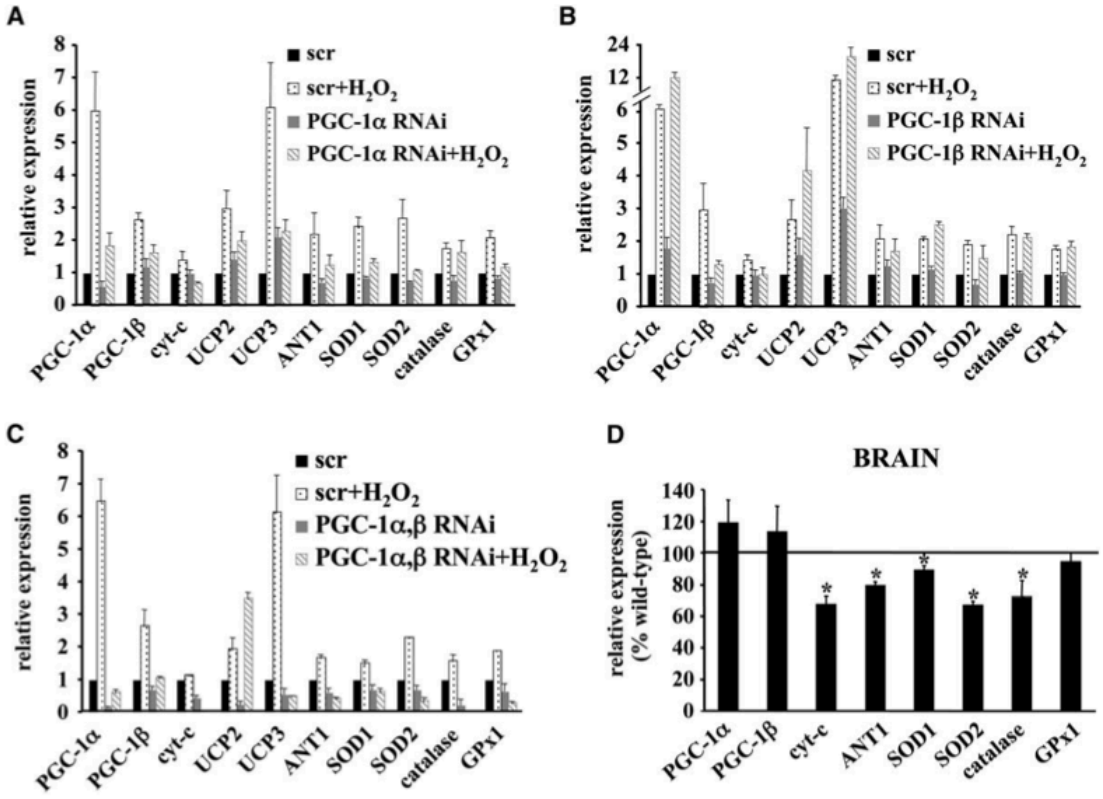


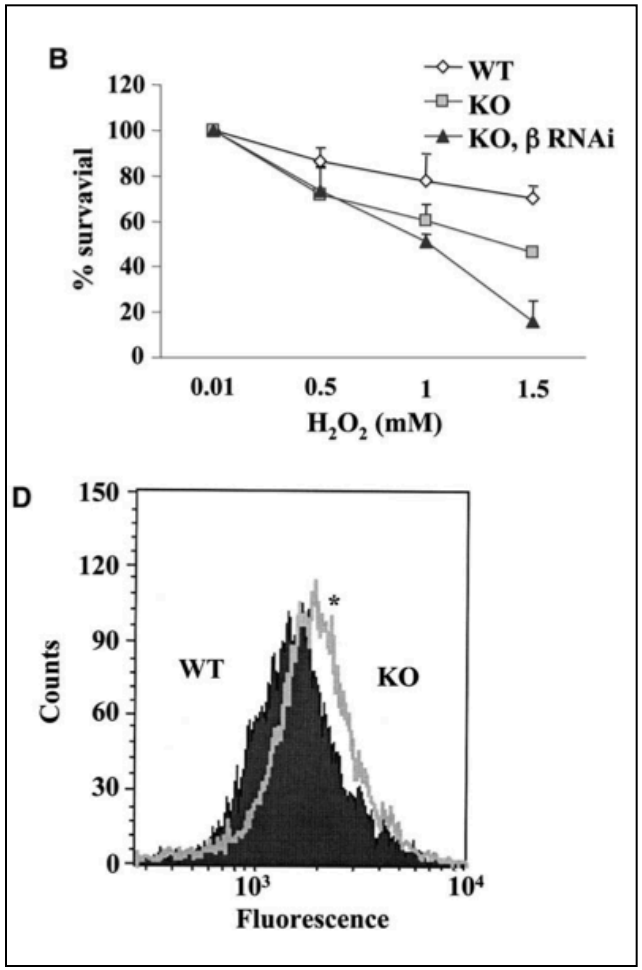
Figure 1. PGC-1α and PGC-1β Regulate Genes of the ROS Defense System

(A) 10T1/2 cells were infected with RNAi against PGC-1α or with scrambled controls. After 3 days, cells were treated with 1 mM H_2O_2 for 2 hr followed by a recovery period of 2 hr. Cells were then harvested for RNA isolation, and relative expression of PGC-1s and uncouplers as well as mitochondrial, cytoplasmic, and peroxisomal ROS-detoxifying enzymes was measured by real-time PCR. In this and all other figures, error bars represent means ± SEM. n = 3.

(B) 10T1/2 cells were infected with RNAi against PGC-1β or with scrambled controls. Cells were treated and analyzed as described above.

(C) 10T1/2 cells were infected with RNAi against both PGC-1α and PGC-1β or with scrambled controls. Cells were treated and analyzed as described above.

(D) The relative expression of various components of the ROS defense system were determined by real-time PCR analysis in the brain of *PGC-1α* null mice compared with WT controls. n = 3–4. * denotes statistical significance compared with WT controls.



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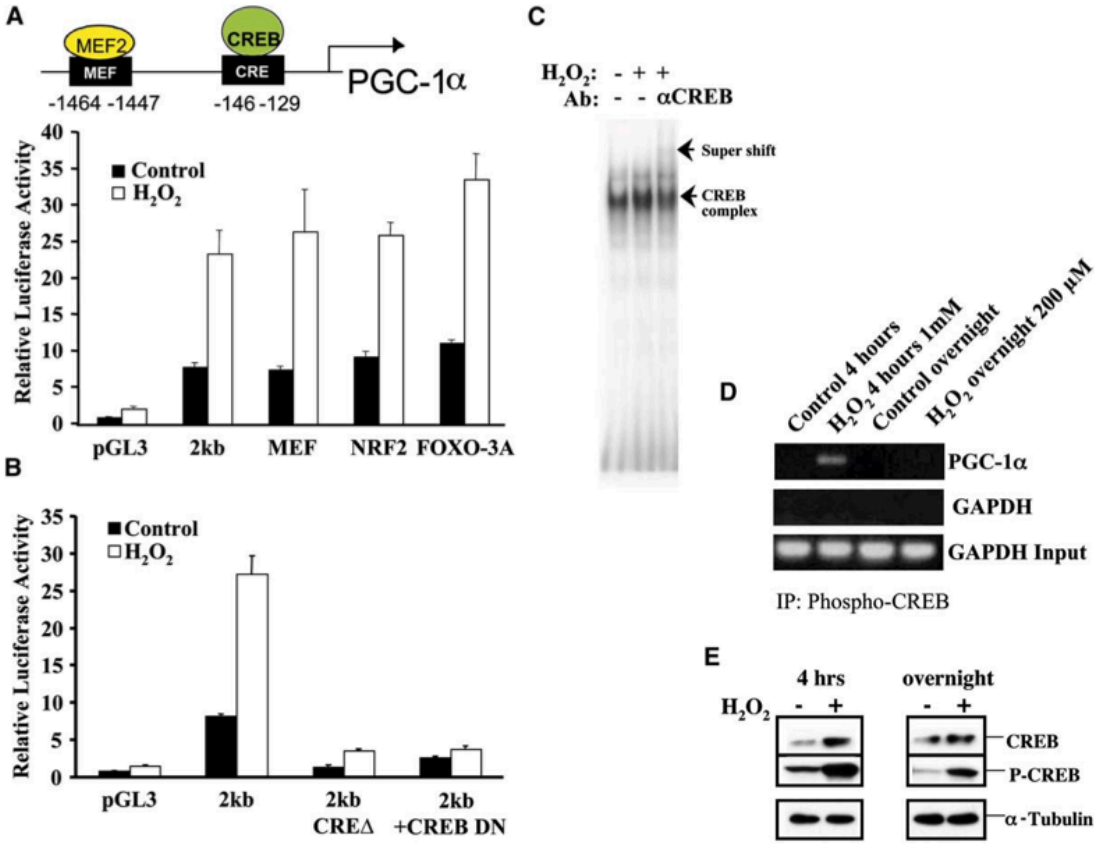


Figure 3. The *PGC-1α* Promoter Is Regulated by CREB in the Presence of H_2O_2

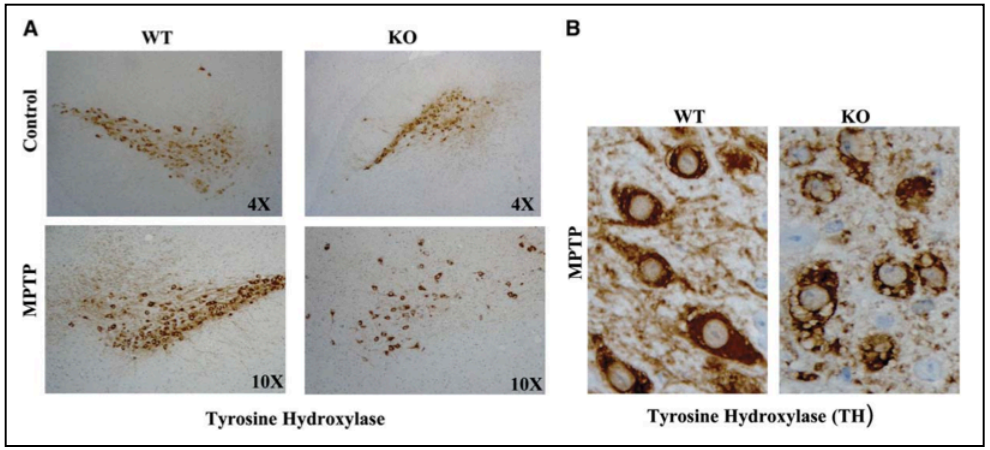
(A) 10T1/2 cells were transfected with the 2 kb *PGC-1α* promoter linked to a luciferase reporter gene harboring no mutations (2 kb) or mutated at the MEF, NRF2, or FOXO3A sites. Cells were treated with vehicle or 1 mM H_2O_2, and luciferase activity was measured 24 hr after transfection. The luciferase activity was normalized to the level of β-galactosidase and to the activity of an empty pGL3basic reporter gene vector. n = 4.

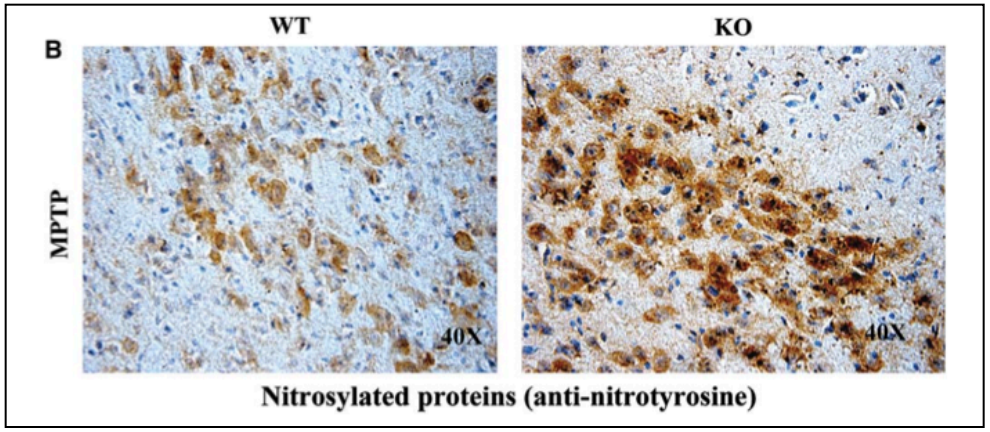
(B) 10T1/2 cells were transfected with the 2 kb *PGC-1α* promoter linked to a luciferase reporter gene harboring no mutations (2 kb) or a CRE site deletion (2 kb CREΔ) in the presence or absence of vector expressing dominant-negative CREB (CREB DN). As a control, pGL3basic (empty vector) was transfected. Cells were treated and analyzed as described in (A).

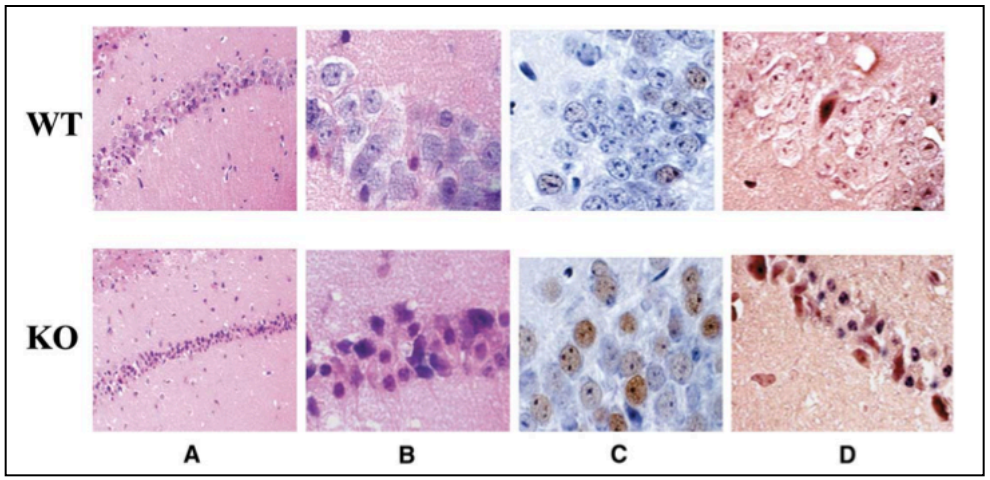
(C) Electrophoretic mobility shift assays were performed with nuclear extracts from 10T1/2 cells treated with or without 1 mM H_2O_2 for 16 hr and radiolabeled probe encoding the CRE-binding site from the *PGC-1α* promoter. Antibodies against CREB were used to test the specificity of the interaction.

(D) Chromatin immunoprecipitation was performed with nuclear extracts from 10T1/2 cells treated with or without H_2O_2 for 4 and 16 hr. Antibody against phospho-CREB was used to precipitate DNA/protein complexes. Specific primers encompassing the CRE-binding site in the *PGC-1α* promoter were used to analyze specific binding to the promoter.

(E) 10T1/2 cells were treated with or without 1 mM H_2O_2 for 2 hr followed by 2 hr recovery or treated with 1 mM H_2O_2 for 16 hr without recovery. Cell lysates were then analyzed using immunoblotting analysis to test for CREB and phosphorylated CREB protein levels. Expression of α-tubulin was used as loading control.







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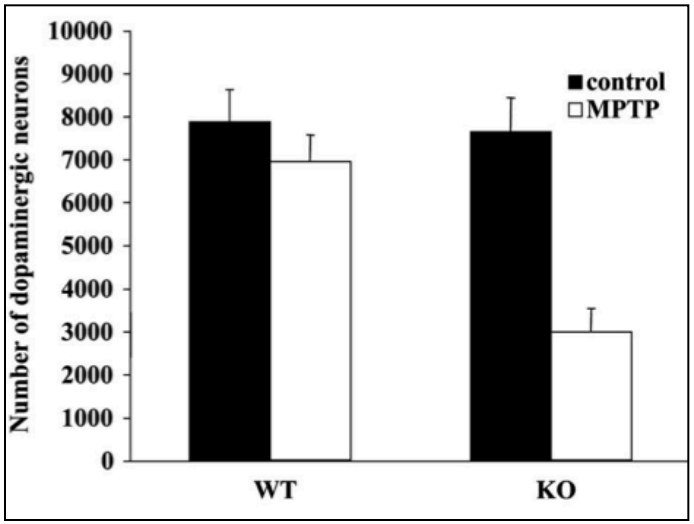

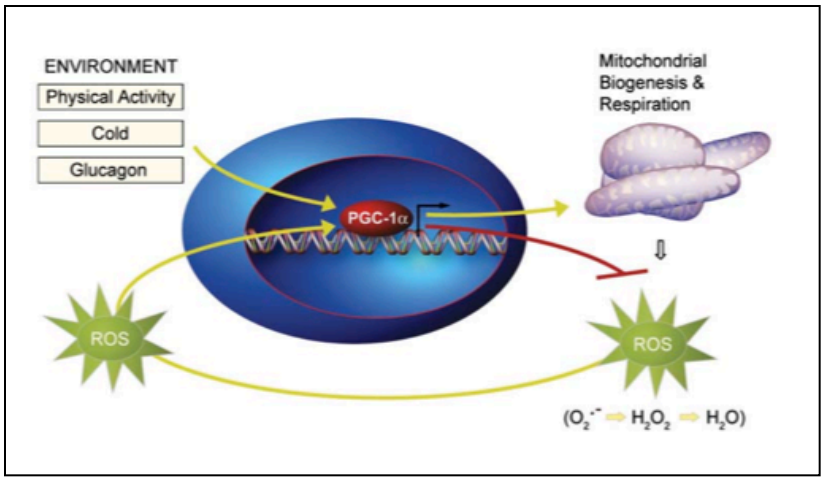

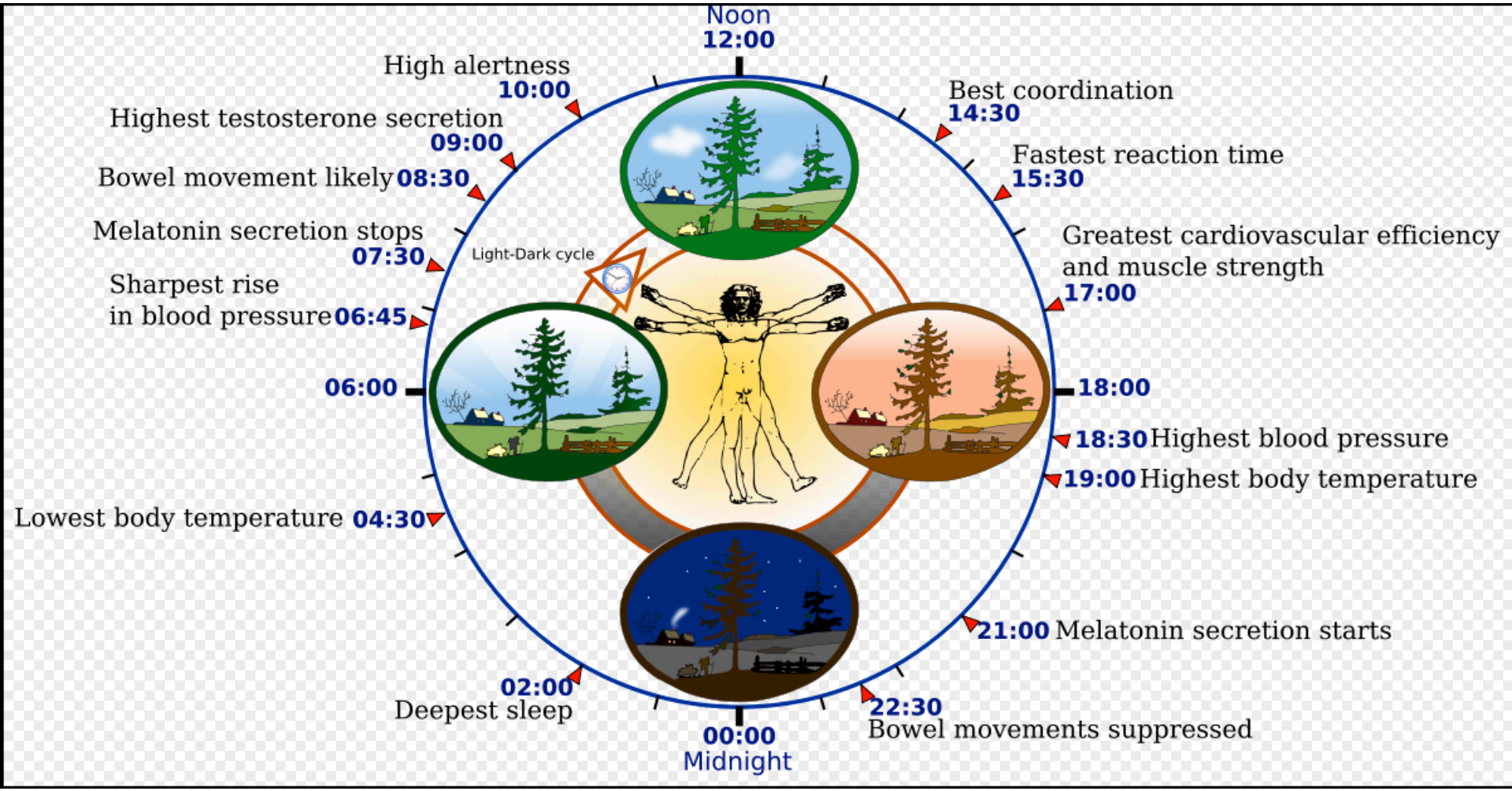
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Deepest sleep
00:00
Midnight
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Highest blood pressure
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17:00
Greatest cardiovascular efficiency
and muscle strength
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Fastest reaction time
14:30
Best coordination
Light-Dark cycle