Institut de Neurociències
UNIVERSITAT DE BARCELONA

FACULTAT DE FARMÀCIA

The SAMP8 Mouse Model: Linking neurodegeneration in aging with epigenetics

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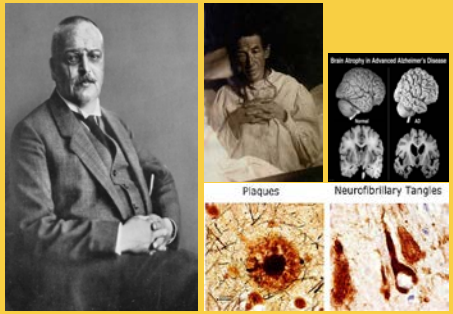
Neuropharmacology in aging and Neurodegeneration
Faculty of Pharmacy and Food Sciences
June 19th, 2018

UNIVERSITAT DE BARCELONA

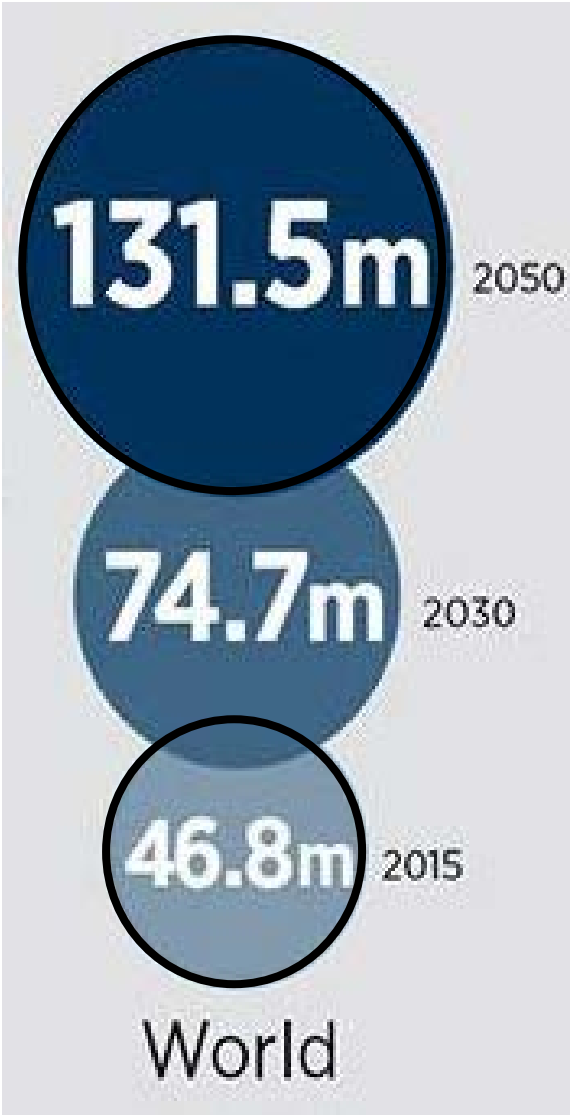
Age Related Diseases

Alzheimer's Disease

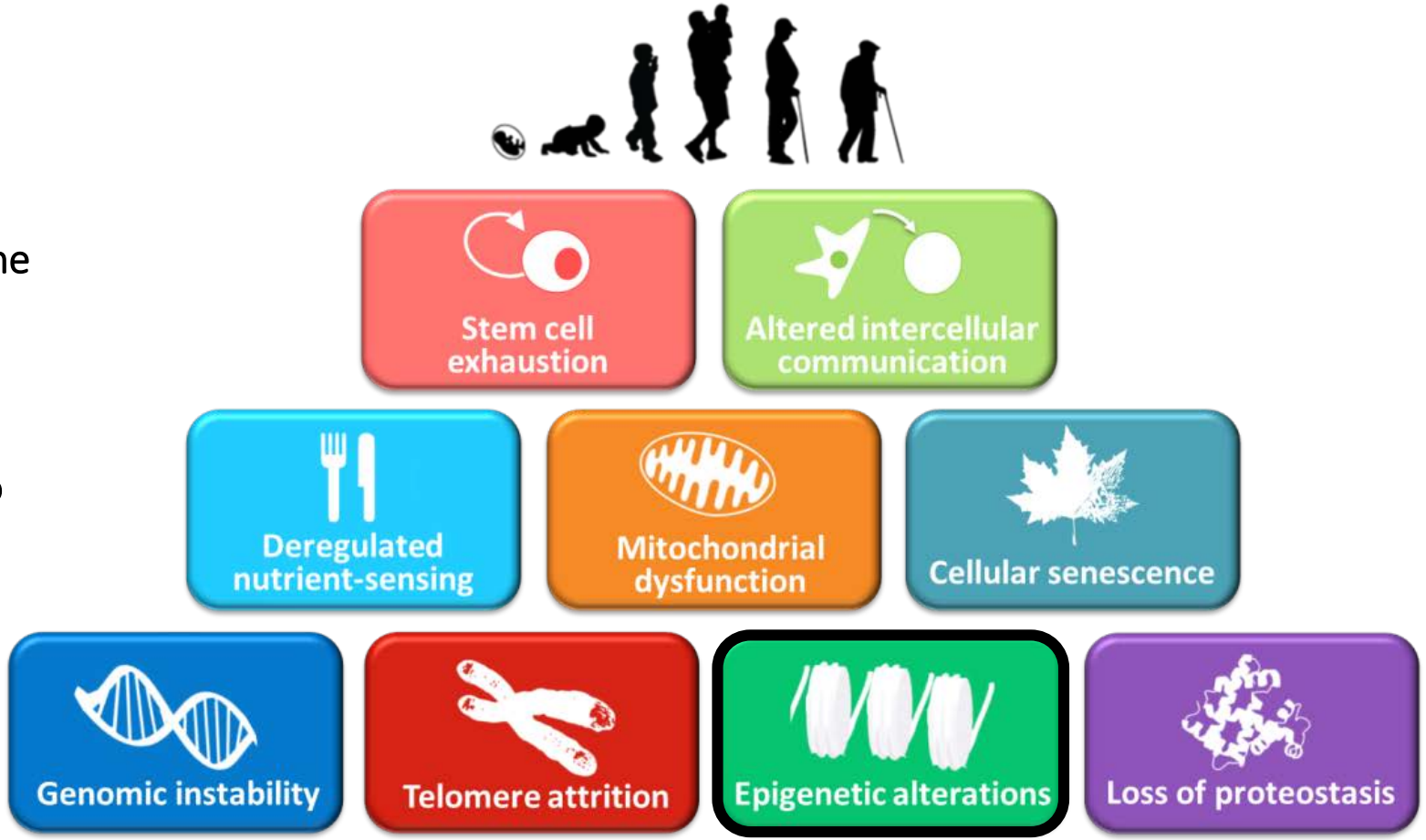


- The most common cause of dementia
- Neurodegenerative disease
- Progessive and Irreversible
- Cognitive Impairment and behavioural abnormalities
- Neuropathological alterations: β-amyloid, Tau hyperphosphoryation and cell death.
- Sporadic Alzheimer's disease 99% of cases

The greatest risk factor for AD is advanced age



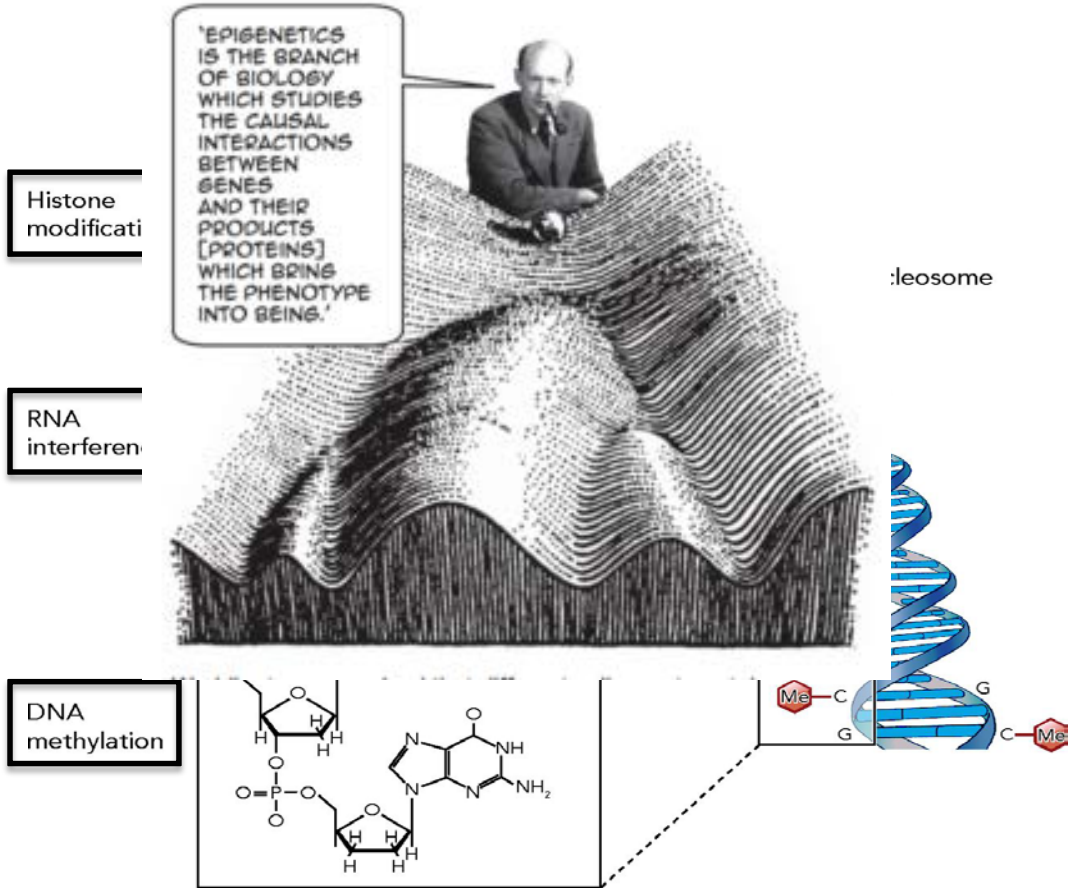
The hallmarks of aging



The hallmarks of aging, López-Otín et al., Cell 2013

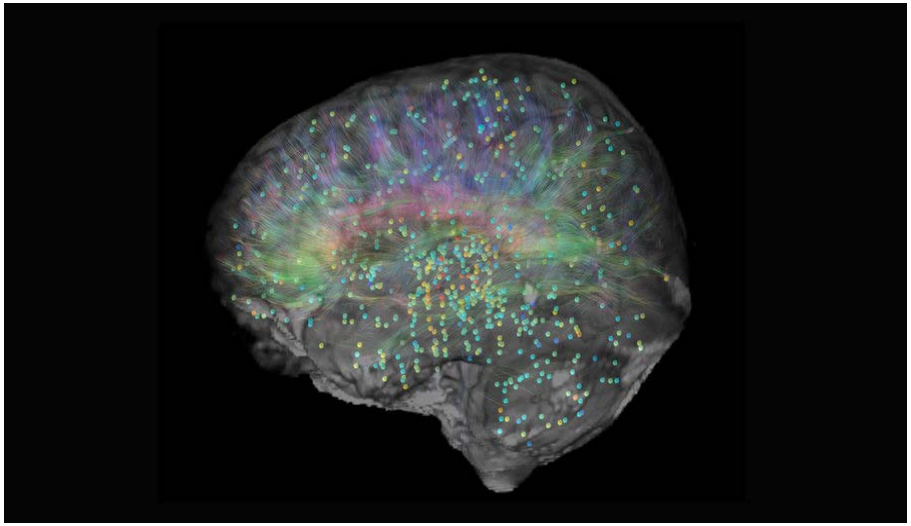
Epigenetic mechanisms

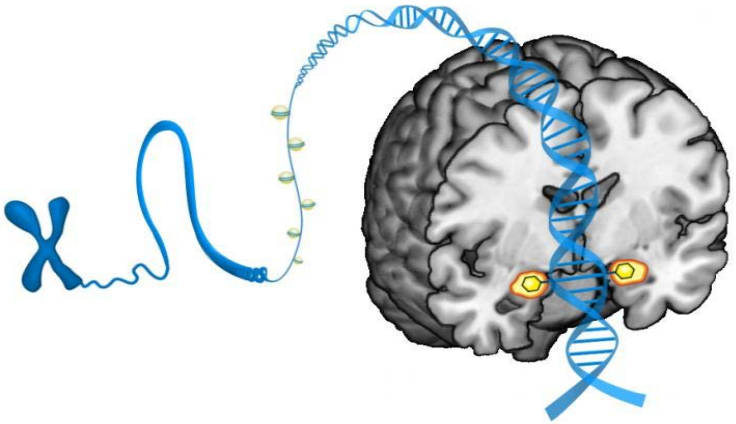
A consensus definition of the concept of *epigenetic trait* as "**stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence**" was formulated at a Cold Spring Harbor meeting in 2008.



Beyond the Genome: Epigenetic Mechanisms in Lung Remodeling. Physiology. James S. Hagood, 2014.

Epigenetics and Brain





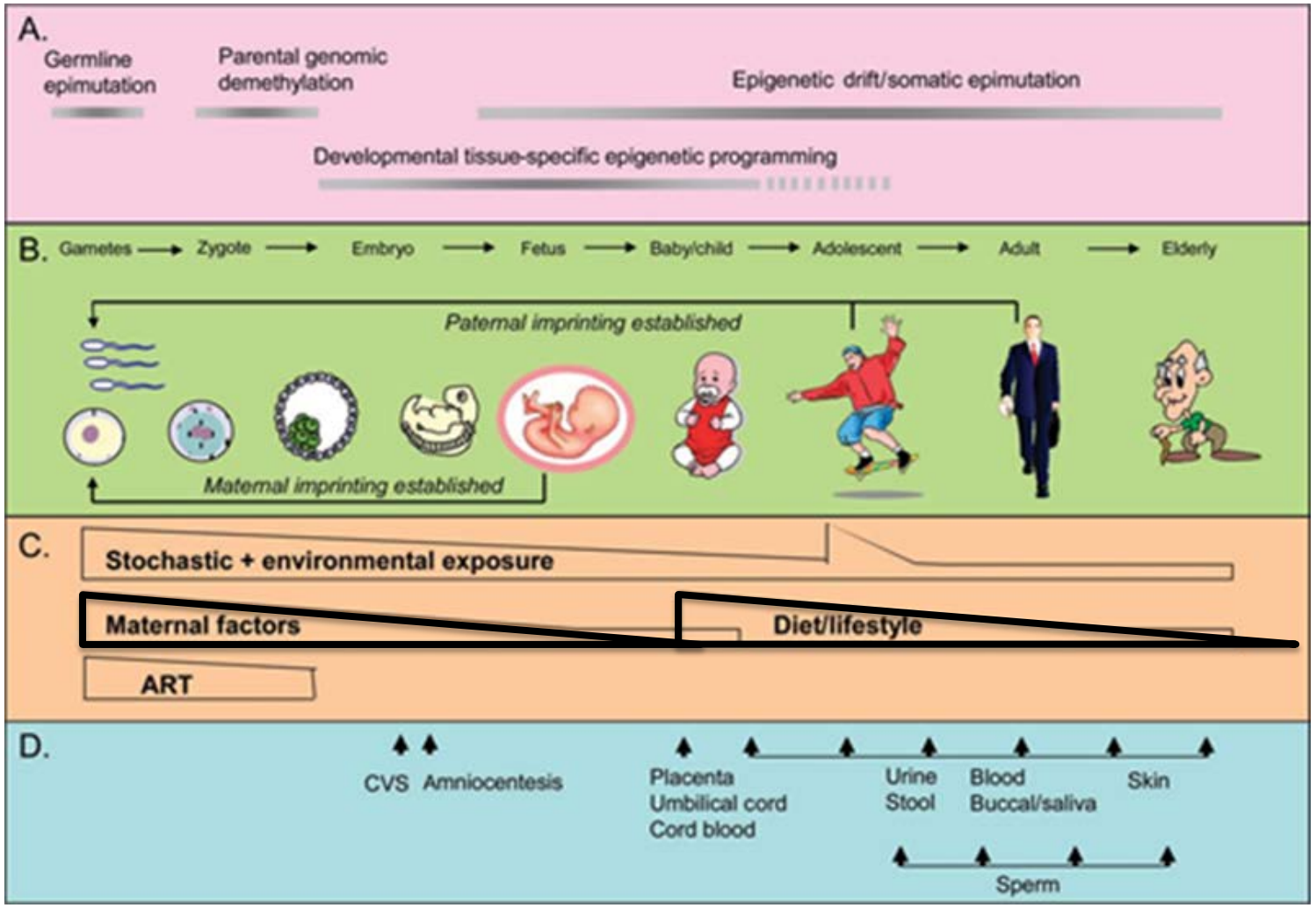
The human brain expresses numerous genes; approximately 80–95% of protein-coding genes are expressed in at least one brain region during at least one period of development or adulthood.

One the most important findings that supports the importance of epigenetics in the functioning of the brain has been the discovery that neuronal activity *per se* modifies DNA methylation and histone modifications patterns, and further, that learning and memory depend on these epigenetic changes.

Bae B, Jayaraman D, Walsh CA. Genetic Changes Shaping the Human Brain. *Developmental cell*. 2015;32(4):423-434.

Levenson J. M., Sweatt J. D. (2005). Epigenetic mechanisms in memory formation. *Nat. Rev. Neurosci.* 6 108–118.

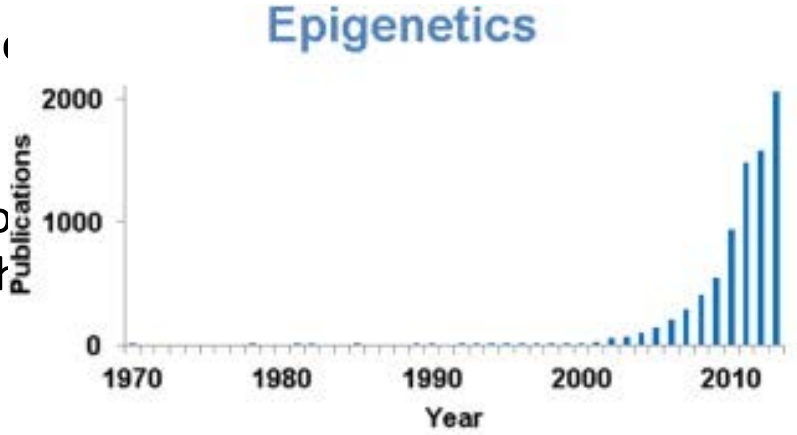
Epigenetics and life



What causes AD?

Th torial.

It is produced by a added to exposure to environmental facto interact, in a prolonged temporary sale th ferent effect on each



Contents lists available at ScienceDirect
Ageing Research Reviews
journal homepage: www.elsevier.com/locate/arr

Review

Epigenetic mechanisms in Alzheimer's disease: Implications for pathogenesis and therapy

Jun Wang[a], Jin-Tai Yu[a,b,c,**], Meng-Shan Tan[b], Teng Jiang[c], Lan Tan[a,b,c,*]

Contents lists available at ScienceDirect
Progress in Neurobiology
journal homepage: www.elsevier.com/locate/pneurobio

Epigenetic regulation in the pathophysiology of Alzheimer's disease

Leonidas Chouliaras[a,1], Bart P.F. Rutten[a,1,*], Gunter Kenis[a], Odette Peerbooms[a], Pieter Jelle Visser[a,b], Frans Verhey[a], Jim van Os[a,c], Harry W.M. Steinbusch[a], Daniel L.A. van den Hove[a,d]

Contents lists available at ScienceDirect
Progress in Neuro-Psychopharmacology & Biological Psychiatry
journal homepage: www.elsevier.com/locate/pnp

Epigenetics in neurodegeneration: A new layer of complexity

Sueli C.F. Marques[a,b,c], Catarina R. Oliveira[c,d], Claudia M.F. Pereira[c,d], Tiago F. Outeiro[b,e,*]

Contents lists available at ScienceDirect
Neurobiology of Aging
journal homepage: www.elsevier.com/locate/neuaging

Review

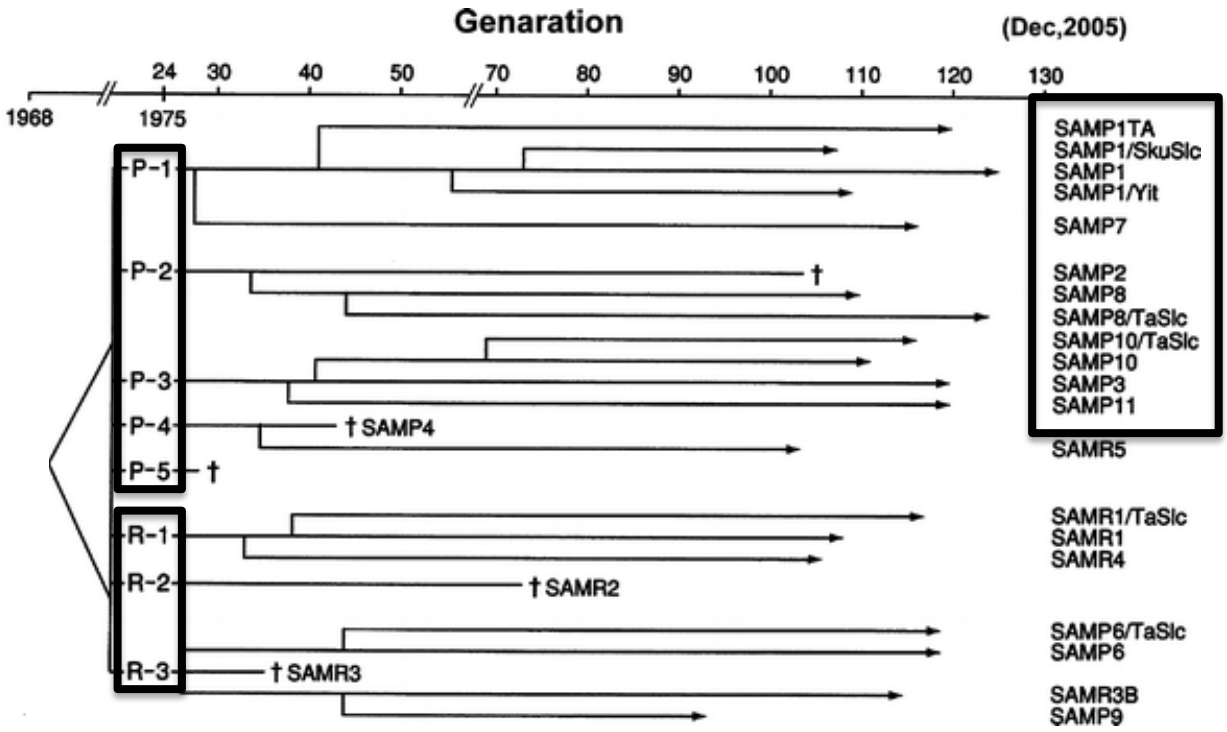
Epigenetically regulated microRNAs in Alzheimer's disease

Daniel L. Van den Hove[a,b,*], Konstantinos Kompotis[a], Roy Lardenoije[a], Gunter Kenis[a], Jonathan Mill[c,d], Harry W. Steinbusch[a], Klaus-Peter Lesch[a,b], Carlos P. Fitzsimons[e], Bart De Strooper[f,g], Bart P.F. Rutten[a]

The SAMP8 Mouse Model

Dr. Takeda 1968

AKR/J strain



SAM resistant (SAMR) mice

Median survival 16.3 months

SAM prone (SAMP) mice

Median survival 9.7 months

The SAMP8 Mouse Model

CHARACTERISTICS OF AGE-RELATED BEHAVIORAL CHANGES IN SENESCENCE-ACCELERATED MOUSE SAMP8 AND SAMP10

MASAOMI MIYAMOTO

Pharmaceutical Research Laboratories 1, Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., 2-17-85, Jusohonmachi, Yodogawa-ku, Osaka 532, Japan

Molecular Genetic Characterization of the Senescence-Accelerated Mouse (SAM) Strains

Haruo Kitado, Keiichi Higuchi, Toshio Takeda

Journal of Gerontology, Volume 49, Issue 6, 1 November 1994, Pages B247–B254,
https://doi-org.sire.ub.edu/10.1093/geronj/49.6.B247
Published: 01 November 1994 **Article history ▾**

GENETIC CHARACTERIZATION OF SENESCENCE-ACCELERATED MOUSE (SAM)

KEIICHI HIGUCHI

Department of Senescence Biology, Chest Disease Research Institute, Kyoto University, Sakyo-ku, Kyoto 606 Japan

RESEARCH ARTICLE Open Access

Exome sequencing of senescence-accelerated mice (SAM) reveals deleterious mutations in degenerative disease-causing genes

Kumpei Tanisawa[1,2], Eri Mikami[1,2,3], Noriyuki Fuku[1], Yoko Honda[1], Shuji Honda[1], Ikuro Ohsawa[4], Masafumi Ito[5], Shogo Endo[6], Kunio Ihara[7], Kinji Ohno[8], Yuki Kishimoto[9], Akihito Ishigami[9], Naoki Maruyama[9], Motoji Sawabe[10], Hiroyoshi Iseki[11], Yasushi Okazaki[11], Sanae Hasegawa-Ishii[12], Shiro Takei[12], Atsuyoshi Shimada[12], Masanori Hosokawa[12], Masayuki Mori[13], Keiichi Higuchi[13], Toshio Takeda[14], Mitsuru Higuchi[15] and Masashi Tanaka[1*]

of lungs,

and

Research

Open Access

Mechanisms of aging in senescence-accelerated mice

Todd A Carter[¤*], Jennifer A Greenhall[¤*], Shigeo Yoshida[†], Sebastian Fuchs[*], Robert Helton[*], Anand Swaroop[†‡], David J Lockhart[§] and Carrolee Barlow[*]

Addresses: [*]The Salk Institute for Biological Studies, La Jolla, CA 92037, USA. [†]Department of Ophthalmology and Visual Sciences, University of Michigan, Ann Arbor, MI 48105, USA. [‡]Department of Human Genetics, University of Michigan, Ann Arbor, MI 48105, USA. [§]Ambit Biosciences, San Diego CA 92121, USA. [¤]Current address: BrainCells Inc., 10835 Road to the Cure, San Diego, CA 92121, USA.

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Experimental Gerontology 40 (2005) 774–783
Experimental Gerontology
www.elsevier.com/locate/expgero

Mini review

The senescence-accelerated prone mouse (SAMP8): A model of age-related cognitive decline with relevance to alterations of the gene expression and protein abnormalities in Alzheimer's disease

D. Allan Butterfield*, H. Fai Poon

Review Article

Senescence-Accelerated Mice P8: A Tool to Study Brain Aging and Alzheimer's Disease in a Mouse Model

Mercè Pallàs

NEUROPATHOLOGY
Neuropathology 2017; **37**, 293–305 doi:10.1111/neup.12373

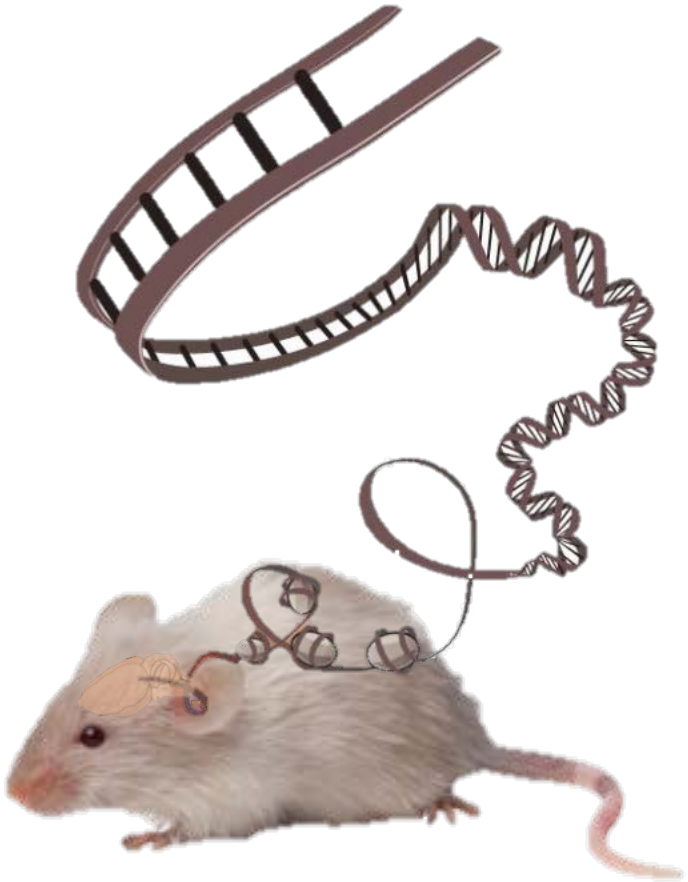
Occasional Review

SAMP8 mice as a neuropathological model of accelerated brain aging and dementia: Toshio Takeda's legacy and future directions

Ichiro Akiguchi,[1,2] Mercè Pallàs,[10] Herbert Budka,[11] Haruhiko Akiyama,[4] Masaki Ueno,[5] Jingxian Han,[12] Hideo Yagi,[1] Tomohumi Nishikawa,[2] Yoichi Chiba,[5] Hiroshi Sugiyama,[3] Ryoya Takahashi,[6] Keiko Unno,[7] Keiichi Higuchi[8] and Masanori Hosokawa[9]

The SAMP8 Mouse Model

Epigenetics can explain in part the senescent phenotype that characterizes SAMP8



frontiers in AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 20 March 2014
doi: 10.3389/fnagi.2014.00051

Epigenetic alterations in hippocampus of SAMP8 senescent mice and modulation by voluntary physical exercise

Table 1. Epigenetic alterations presented by SAMP8 in comparison with SAMR1.

Related Aberrant Epigenetic Mark and Regulators	Epigenetic Alteration	References
DNA methylation	Global levels of 5-mC ↑ and 5-hmC ↓	[233]
Histone modifications	H3K24, H3K27, H3K36, H3K79, H3R128, H4K20 and H2AR89 ↓ Global acetylation levels of H3 and H4 ↑	[242]
miRNAs	miR-16, miR-9 and miR-139 ↓	[246, 247, 249]
DNTMs and HDACs	Dnmt3b ↑ Sirt1, Hdac5 and Hdac6 ↓	[233, 25]

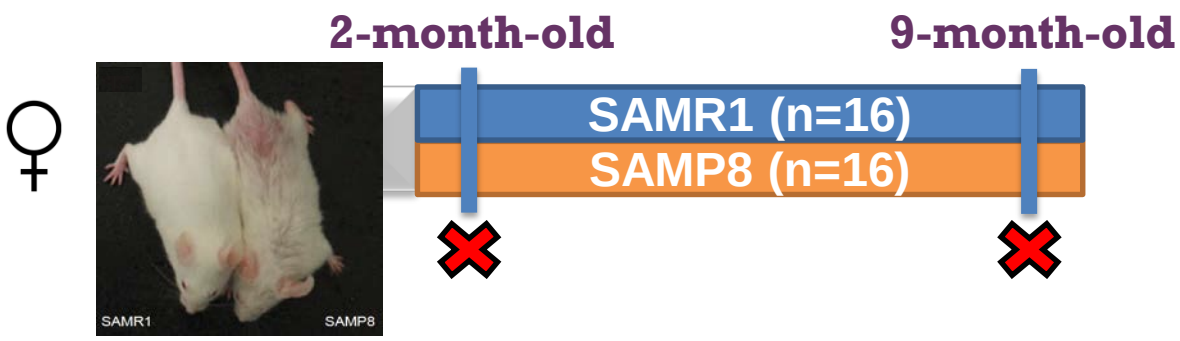
Coral Sanfeliu[a] and Merce Pallas[a,b]
[a]Department of Pharmacology, Toxicology and Therapeutic Chemistry (Pharmacology Section) and Institute of Neuroscience, University of Barcelona and CIBERNED, Barcelona, Spain
[b]Institut d'Investigacions Biomèdiques de Barcelona (IIBB), CSIC, IDIBAPS and CIBERESP, Barcelona, Spain

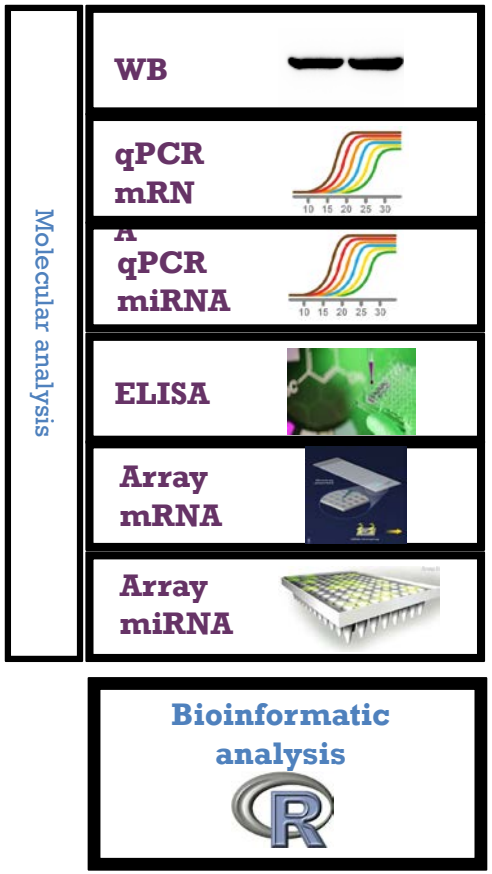
Accepted 11 January 2018

Epigenetic study in SAMP8

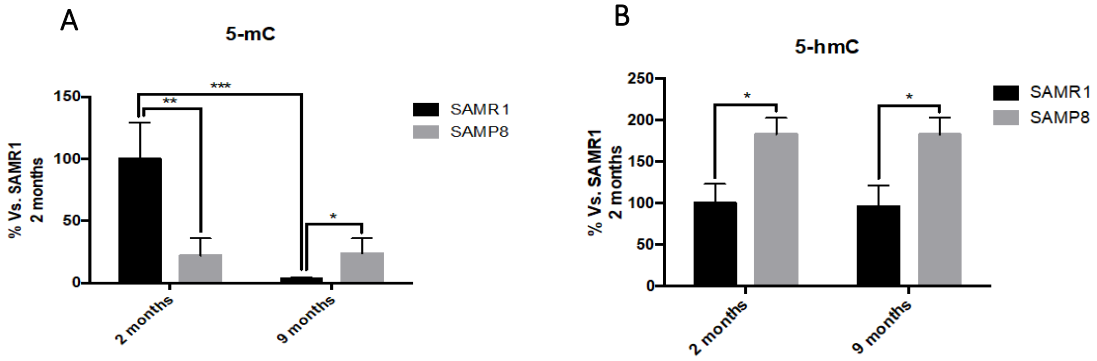
Analysis of early and late-onset epigenetic alterations in female SAMP8 a model of age-related cognitive decline

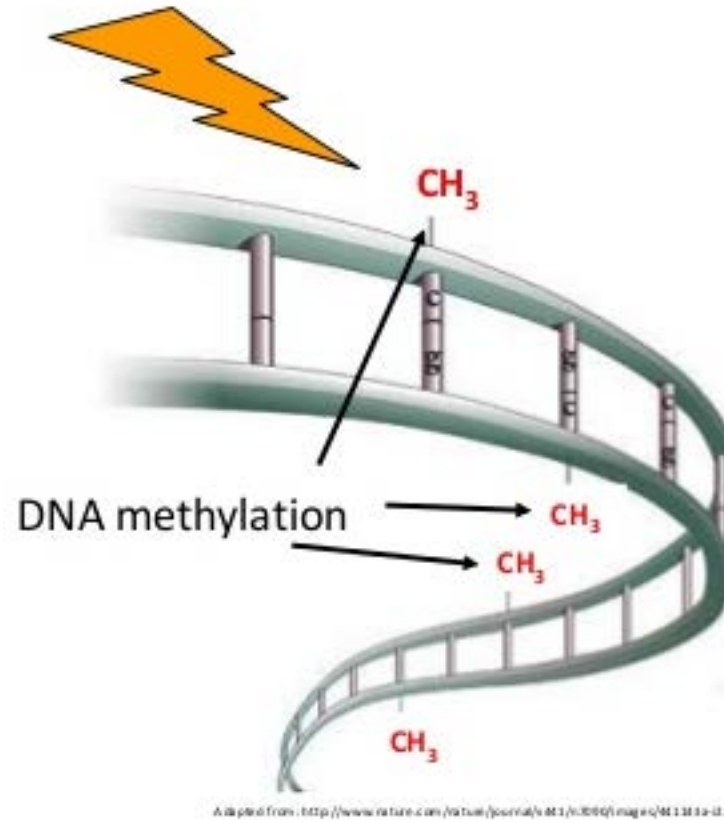
C. Griñán-Ferré[1#], M. Cosín-Tomás[1#], M.J. Álvarez-López[1], J. Companys-Alemany[1], P. Kaliman[1], C. González-Castillo[2], D. Ortuño-Sahagún[2] and M. Pallàs[1].



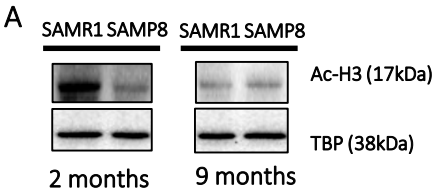


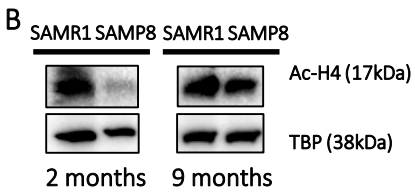
Epigenetic Landscape

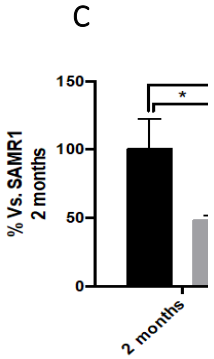




Epigenetic Landscape



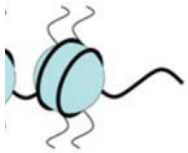


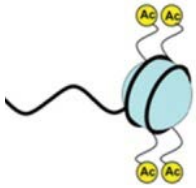


Epigenetics in Alzheimers Disease

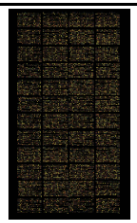
- Animal post-mortem studies show:

Pathology	Effect
Decreased global levels of 5'-mC in brain	Increased Tau phosphorylation
Decreased level of H3 acetylation in Temporal lobe	Decreased synaptic plasticity leading to decreased learning and memory



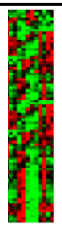


mRNA-miRNA expression



mRNA microarray
SAMR1 2 and 9 months (n=6)
SAMP8 2 and 9 months (n=6)

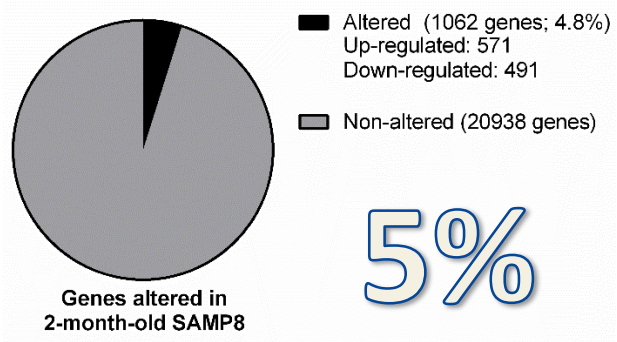
1,062 mRNAs differentially expressed in SAMP8 vs. SAMR1 at 2 months
1,033 mRNAs differentially expressed in SAMP8 vs. SAMR1 at 9 months
92 mRNAs differentially expressed in both 2 and 9 months
(Figure 1 and Suppl. Material 3)



microRNA PCR array
SAMR1 2 and 9 months (n=6)
SAMP8 2 and 9 months (n=6)

28 miRNAs differentially expressed in SAMP8 vs. SAMR1 at 2 months
17 miRNAs differentially expressed in SAMP8 vs. SAMR1 at 9 months
6 miRNAs differentially expressed in both 2 and 9 months
(Figure 4 and Suppl. Material 4)

mRNA-miRNA expression



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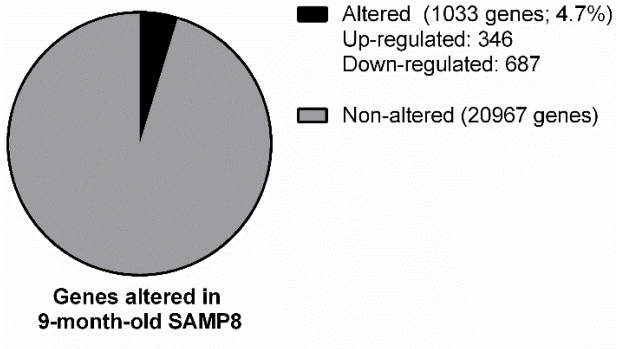

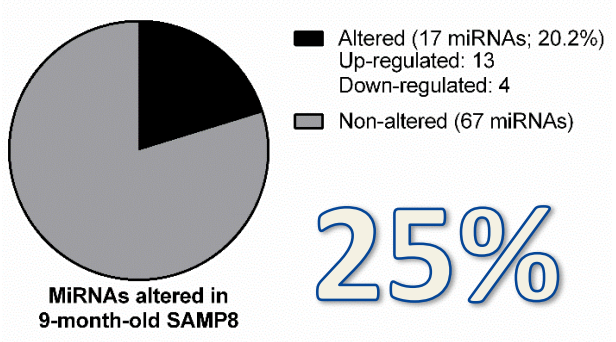

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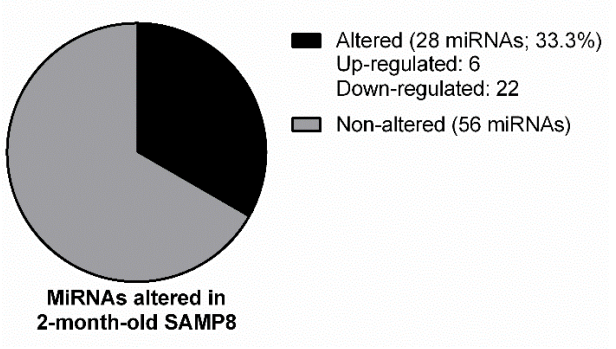
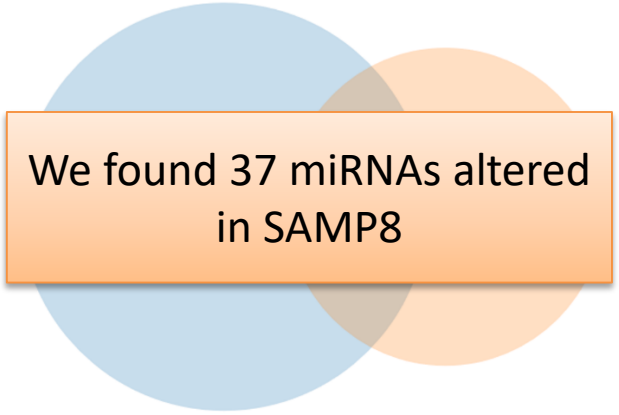


We found 174 mRNA targets altered in SAMP8



We found 37 miRNAs altered in SAMP8

Regulatory networks

A

B

C

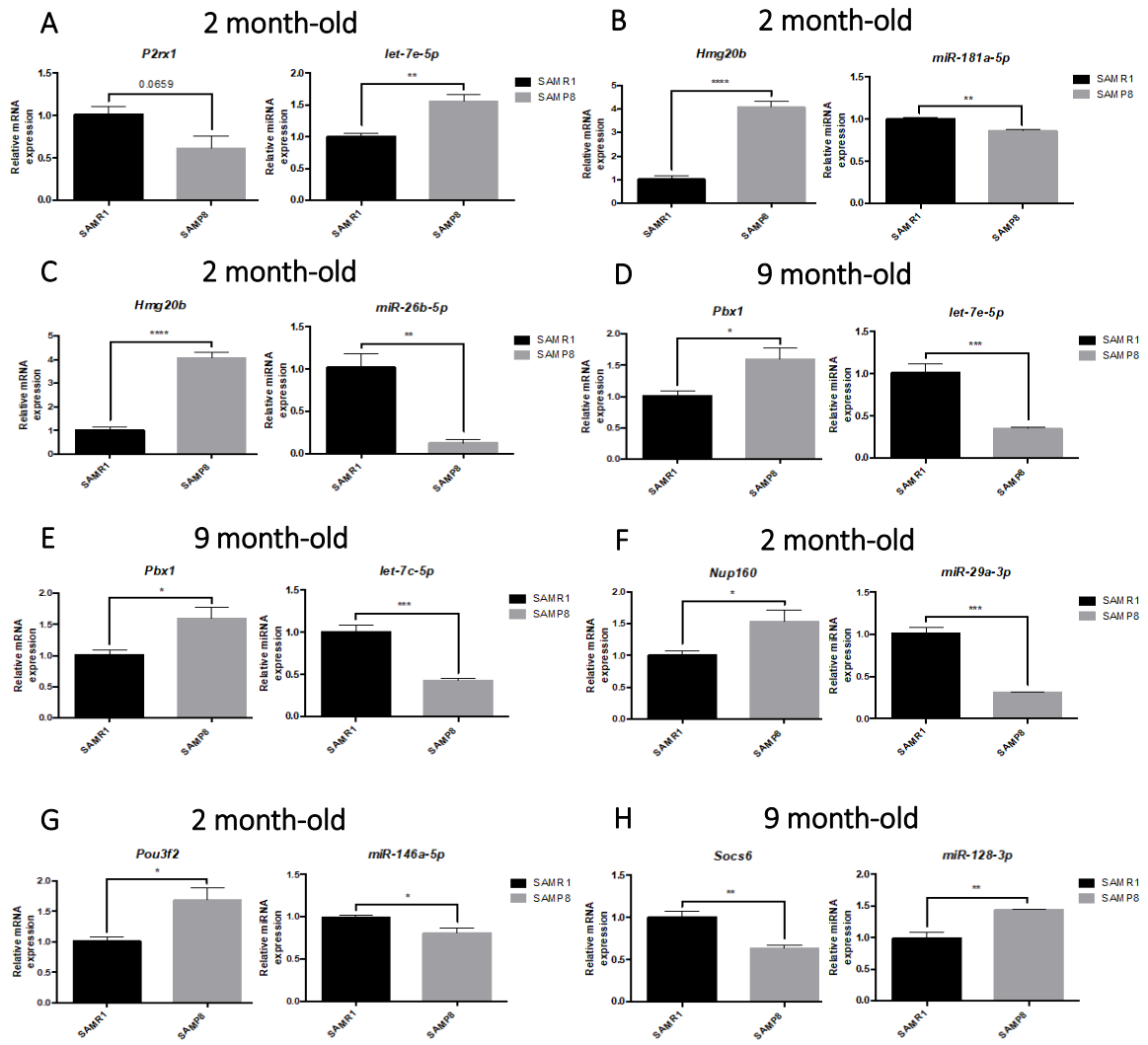
	MicroRNAs	Target mRNAs	Top 10 GO Biological process	p-value	Z-score	Combined score
9-month-old SAMP8, miRNAs up:mRNAs down	*mmu-miR-128-3p, mmu-miR-140-5p, mmu-miR-148b-3p, mmu-miR-342-3p, mmu-miR-98-5p, mmu-miR-107-3p*	*Capza2, Cav1, Chuk, Dll3, Drd4, Pdia3, Gcdh, Gria1, H3f3b, Htr1f, Kcnj8, Dnajc3, Clpb, Itga5, Itk, Cyth3, Hsp90b1, Hs2st1, Spry4, Map2k7, Fgf9, Atp11a, Mapk6, Slc5a3, Socs6, Thsd1, B3galtn1, Kcna4, Txnip, Vps50, Arl4d, Cdip1, Mmachc, Ergic1, Chac2, Cttnbp2nl, Gpr63.*	Memory (GO: 0007613)	0.001378	-2.23	4.11
			Response to tumor necrosis factor (GO: 0034612)	0.002467	-2.31	3.96
			Synaptic transmission (GO: 0007268)	0.003559	-2.32	3.88
			Activation of innate immune response (GO: 0002218)	0.005741	-2.21	3.70
			Learning or memory (GO:0007611)	0.01189	-2.20	3.63
			Cognition (GO: 0050890)	0.01703	-2.16	3.57
			Positive regulation of canonical Wnt signaling pathway (GO: 0090263)	0.009200	-2.11	3.49
			Cellular response to unfolded protein (GO: 0034620)	0.01849	-2.01	3.32
			Neuron-neuron synaptic transmission (GO: 0007270)	0.008912	-2.01	3.32
			Response to carbohydrate (GO: 0009743)	0.04411	-1.89	3.11
2-month-old SAMP8, miRNAs down:mRNAs up	*mmu-let-7b-5p, mmu-let-7c-5p, mmu-let-7d-5p, mmu-let-7e-5p*	*Ncoa3, Pbx1, Mxd1, Pald1, Trp53rk, Klhl13.*	Positive regulation of cell cycle G2/M phase transition (GO:1902751)	0.004199	-2.74	9.30
			Positive regulation of G2/M transition of mitotic cell cycle (GO:0010971)	0.004199	-2.74	9.29
			Positive regulation of mitotic cell cycle (GO:0045931)	0.02884	-2.15	6.24
			Intracellular steroid hormone receptor signaling pathway (GO:0030518)	0.02059	-2.07	6.09
			Negative regulation of sequence-specific DNA binding Transcription factor activity (GO:0043433)	0.03514	-2.10	5.95
			Histone acetylation (GO:0016573)	0.02829	-2.05	5.93
			Developmental growth (GO:0048589)	0.04520	-2.16	5.83
			Negative regulation of neuron differentiation (GO:0045665)	0.04085	-2.15	5.83
			Positive regulation of cell cycle process (GO:0090068)	0.06054	-2.29	5.74
			Negative regulation of neurogenesis (GO:0050768)	0.05032	-2.14	5.56

MicroRNAS	Target mRNAs	Top 10 GO Biological process	p-value	Z-score	Combined score
mmu-miR-298-5p, mmu-miR-151-3p	*Adss, Ctnnd1, Comt1, Cyp7b1, Flt4, ... Pcp4, Nptn, Sepp1, Slc17a1, Atp8a1,*	Regulation of membrane lipid distribution (GO: 0097035)	0.002603	-2.53	4.08
		Cellular response to extracellular stimulus (GO: 0031668)	0.002990	-2.26	3.66
		Synapse organization (GO: 0050808)	0.005018	-2.06	4.07

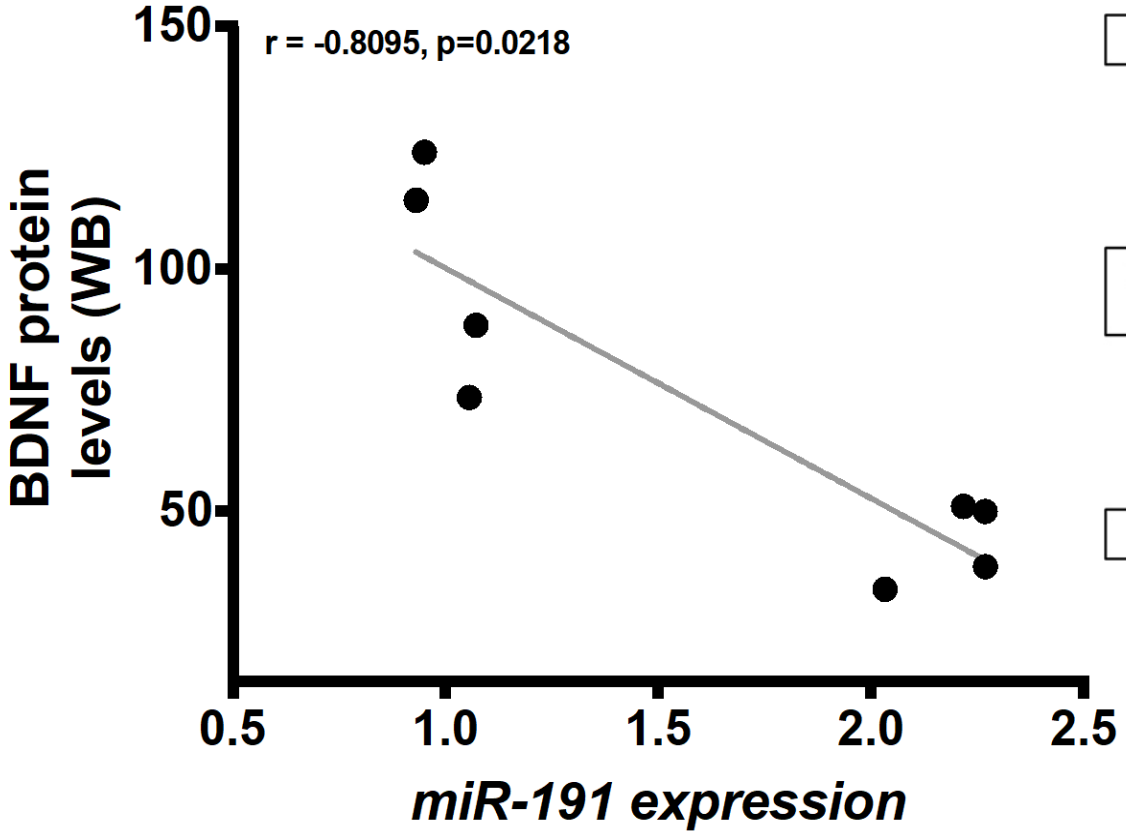
Mmp9, Pam, Pax6, Sh3yl1, Mga, Rasal1, Slc33a1, Dkk3, Galns, Dnajc5, Irf6, Slc5a3, Chst2, Cldn8, Grpbp2, Rbms2, Plp2, Amotl2, Cyp2d22, Stx5a, C1qtnf1, Pnkd, Insm2, Srf, Nup160, Rhot1, Midn, Tsc1, Cmtm3, Tceanc2, Srek1ip1, Fbxo32, Nacc2, Efcab2.

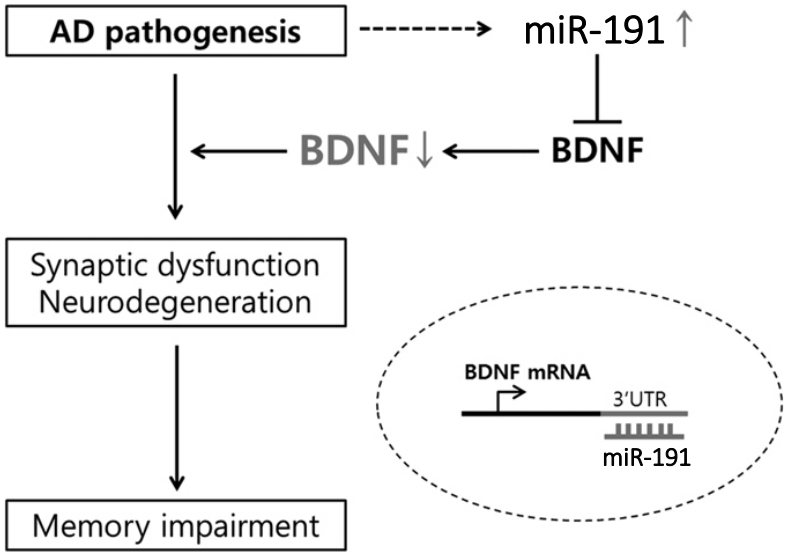
Validation of mRNA:miRNA

The selected mRNA:miRNA pairs are involved in brain aging and neurodegeneration.



Validation of mRNA:miRNA





Conclusions

Our data indicate the reciprocal interaction between non-genetic factors and epigenetic mechanisms that can explain the senescence process in the SAMP8, and specifically the main role of miRNA in gene regulation, supported their use as biomarkers for aging and their importance for developing novel therapeutic interventions for AD, based on epigenetics.

THANK YOU!

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