Epigenetics and Cognitive Aging

J. David Sweatt

Science **328**, 701 (2010);
DOI: 10.1126/science.1189968

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published weekly, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005.

numbers are encouraging for 0.67-μm layer thickness, and of course better for 0.2 μm. In this case, all modules could be CdTe. For the 25% PV electricity in 2030, the goal could be reached with 0.2-μm layers.

So this analysis brings us back to the question—will CdTe contribute substantially to renewable energy production? Supply and demand will almost certainly remain a key issue in CdTe PV production. However, projections that underestimate CdTe PV at this early stage of development assume a situation for Te supply and use that will be nearly static during the next 20 years. In an area driven by innovation, this grim scenario seems unlikely.

References and Notes

1. B. L. Cohen, *Geochim. Cosmochim. Acta* **48**, 203 (1984).
2. First Solar accounts for almost all production of CdTE moldules at this time. Abound Solar has had some production in 2010. PrimeStar Solar–GE, Q-Cells Calyxo, and Arendi are CdTe PV startup companies that remain largely precommercial.
3. U.S. Energy Information Administration, *Electric Power Monthly*, March 2010, http://tonto.eia.doe.gov/ftproot/electricity/epm/02261003.pdf.
4. First Solar has a technical roadmap that would reduce near-term costs by one-third. However, silicon module costs have plunged recently, so that the cost difference between First Solar products and the best of the silicon products, many from China, is now small—perhaps 20% at the system level.
5. M. A. Green, *Prog. Photovoltaics* **14**, 743 (2006).
6. V. Fthenakis, *Renewable Sustainable Energy Rev.* **13**, 2746 (2009).
7. J. R. Hein, A. Koshchinsky, A. N. Halliday, *Geochim. Cosmochim. Acta* **67**, 1117 (2003).
8. F. Ojebuoboh, *World Metallurgy—ERZMETALL*—Heft 1/2008 **61**, 1 (2008).
9. W. C. Cooper, Ed., *Tellurium* (Van Nostrand, New York, 1971), chap. 1.
10. "Mexivada stakes new gold-tellurium property in Mexico," Press Release, 12 June 2008 (www.mexivada.com).
11. Sichuan Apollo Solar T&D Inc., 2008, www.scasolar.com/english/web.asp?id=186 (accessed 11 June 2008).
12. Gold Ore Resources, http://metalsplace.com/news/articles/24830/gold-ore-announces-positive-tellurium-metallurgical-studies (2009).
13. It is a mystery why there is so much tellurium in the universe (*1*) and so little found on Earth. Do the undersea ridges explain the crustal absence? Or is there much more, elsewhere, waiting to be found?

14. The author was a cofounder of PrimeStar Solar. George Washington University Solar Institute is a member of Thin Film PV Partnership and receives financial support from First Solar.

10.1126/science.1189690

NEUROSCIENCE

Epigenetics and Cognitive Aging

Changes in the epigenetic modification of chromatin may be the molecular basis for memory decline in aging adults.

J. David Sweatt

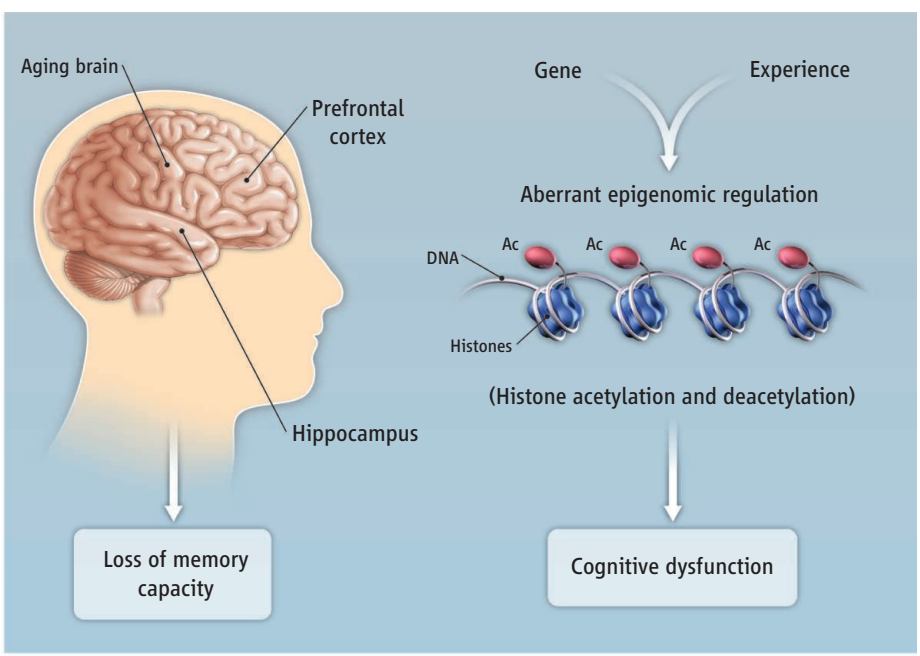
Cognitive decline, especially in memory capacity, is a normal part of aging (*1*). Indeed, the painful reality is that aging-related cognitive decline likely begins when one is in their late 40s. This deterioration is particularly pronounced in declarative memory—the ability to recall facts and experiences—and has been associated with aberrant changes in gene expression in the brain's hippocampus and frontal lobe. However, the molecular mechanisms underlying these changes in gene regulation are not currently known (*2*, *3*). On page 753 of this issue, Peleg *et al*. (*4*) bolster an emerging hypothesis that changes in the epigenetic modification of chromatin in the adult central nervous system drive cognitive decline.

Chromatin remodeling in the hippocampus is necessary for stabilizing long-term memories (*5*–*8*). The relevant molecular mechanisms include DNA methylation and the modification of histone proteins by acetylation, phosphorylation, and methylation. These epigenetic changes involve covalent chemical modifications by enzymes such as histone acetyltransferases and histone deacetylases. Whether alterations in these mechanisms contribute to age-related changes in gene transcription and memory decline are unknown (*8*).

Peleg *et al*. found that aged mice exhibit a disruption of memory-associated activity- and experience-dependent epigenetic modification at the histone H4 lysine 12 (H4K12) acetylation site. This correlated with the loss of almost all normal memory-associated transcription in the hippocampus. Moreover, the authors identified a memory-associated gene, Formin 2 (an actin regulatory protein), and showed that its function is necessary for normal memory, and that its transcriptional regulation is disrupted in aging.

In a final series of studies with potential clinical relevance, Peleg *et al*. show that intrahippocampal infusion of mice with suberoylanilide hydroxamic acid, an inhibitor of histone deacetylase, increased memory-associated H4K12 acetylation in the central nervous system, restored memory-associated transcriptional regulation, and improved behavioral memory function in aged animals.

The study presents a major advance in thinking about the role of histone modifi-



CREDIT: C. BICKEL/*SCIENCE*

Aging and memory. Experience-epigenome interactions may drive memory formation. Decline in this system is a hypothetical basis for cognitive aging.

Department of Neurobiology and Evelyn F. McKnight Brain Institute, University of Alabama at Birmingham, Birmingham, AL 35294, USA. E-mail: dsweatt@uab.edu

cations in synaptic plasticity and memory formation, and ties together three different scientific areas: chromatin regulation, memory-associated transcriptional regulation, and the molecular basis of aging-related cognitive decline. But one cautionary note in considering the work of Peleg *et al*. is to not attribute all of the memory disruption and pharmacological rescue effects in the aged animals to a single histone modification, H4K12 acetylation. Alterations in a large number of chromatin-modifying events likely occur throughout the central nervous system in aging, and improvement of memory as a result of histone deacetylase inhibition is probably due to action at multiple acetylated histone sites. Also, given the possibility of a relevant "histone code" for memory (*9*), even the H4K12 alterations could be tied to another epigenetic mark that is more proximally involved in the aging-associated transcriptional alterations.

There is an emerging understanding that chromatin is dynamic and is subject to extensive experience- and age-associated remodeling (*7*–*15*). For example, global loss of DNA methylation in aging, or the hypermethylation of regulatory regions (promoters) of genes associated with accelerated aging, such as the Werner syndrome and lamin A/C genes, has been proposed to control aging and longevity (*13*). In addition, the sirtuins, a family of nicotinamide adenine dinucleotide (NAD)–dependent histone deacetylases, link chromatin regulation, cellular transformation, and longevity (*14*). And chromatin modifications also regulate telomere-length control, an aging mechanism (*15*). These disparate findings suggest a unifying hypothesis: that the accumulation of aberrant epigenetic marks over the life span drives aging-related cellular and physiological changes.

These considerations have led to a new hypothesis that dysregulation of epigenetic control mechanisms and the accumulation of aberrant epigenetic marks underlie aging-related cognitive dysfunction (*4*, *8*) (see the figure). Specifically, the decreased transcription of key memory-promoting genes during aging is thought to arise from aberrant epigenetic marks and control mechanisms within brain regions particularly vulnerable to the aging process (hippocampus and prefrontal cortex), thus resulting in cognitive deficits. Further pursuit of this unifying hypothesis will require investigating the role of epigenetic molecular mechanisms that control memory formation in aging at two critical loci: histone posttranslational modifications and DNA methylation.

The work of Peleg *et al*. and others (*7*–*9*) constitutes an initial test of the capacity of manipulating the epigenome to potentially reverse aging-associated memory dysfunction, and provide important proof-of-principle studies for evaluating whether this might be a viable approach to therapeutic intervention in cognitive aging. These studies will hopefully lead to more effective prevention strategies to improve quality of life in the aged, as well as contribute to a better understanding of memory function.

References

1. M. S. Albert, R. K. Heaton, in *Geriatric Neuropsychology*, M. S. Albert, M. B. Moss, Eds. (Guilford, New York, 1988), pp. 13–32.
2. S. N. Burke, C. A. Barnes, *Nat. Rev. Neurosci.* **7**, 30 (2006).
3. B. A. Yankner, T. Lu, P. Loerch, *Annu. Rev. Pathol.* **3**, 41 (2008).
4. S. Peleg *et al*., *Science* **328**, 753 (2010).
5. M. W. Swank, J. D. Sweatt, *J. Neurosci.* **21**, 3383 (2001).
6. J. M. Levenson *et al*., *J. Biol. Chem.* **279**, 40545 (2004).
7. T. L. Roth, J. D. Sweatt, *Curr. Opin. Neurobiol.* **19**, 336 (2009).
8. M. R. Penner, T. L. Roth, C. A. Barnes, J. D. Sweatt, *Front. Aging Neurosci.* **2**, 9 (2010).
9. E. Borrelli, E. J. Nestler, C. D. Allis, P. Sassone-Corsi, *Neuron* **60**, 961 (2008).
10. D. Bandyopadhyay, E. E. Medrano, *Exp. Gerontol.* **38**, 1299 (2003).
11. J. M. Sedivy, G. Banumathy, P. D. Adams, *Exp. Cell Res.* **314**, 1909 (2008).
12. C. L. Ramírez, J. Cadiñanos, I. Varela, J. M. Freije, C. López-Otín, *Cell. Mol. Life Sci.* **64**, 155 (2007).
13. M. F. Fraga, M. Esteller, *Trends Genet.* **23**, 413 (2007).
14. V. D. Longo, B. K. Kennedy, *Cell* **126**, 257 (2006).
15. M. A. Blasco, *Nat. Rev. Genet.* **8**, 299 (2007).

10.1126/science.1189968

ENGINEERING

Sewage Treatment with Anammox

Wastewater treatment including high rate anammox processes have the potential to become energy-neutral or even energy-producing.

B. Kartal,[1] J. G. Kuenen,[2] M. C. M. van Loosdrecht[2]

Organic matter must be removed from sewage to protect the quality of the water bodies that it is discharged to. Most current sewage treatment plants are aimed at removing organic matter only. They are energy-inefficient, whereas potentially the organic matter could be regarded as a source of energy. However, organic carbon is not the only pollutant in sewage: Fixed nitrogen such as ammonium (NH_4^+) and nitrate (NO_3^-) must be removed to avoid toxic algal blooms in the environment. Conventional wastewater treatment systems for nitrogen removal require a lot of energy to create aerobic conditions for bacterial nitrification, and also use organic carbon to help remove nitrate by bacterial denitrification (see the figure). An alternative approach is the use of anoxic ammonium-oxidizing (anammox) bacteria, which require less energy (*1*) but grow relatively slowly. We explore process innovations that can speed up the anammox process and use all organic matter as much as possible for energy generation.

The anammox process is responsible for at least 50% of the nitrogen turnover in marine environments (*2*, *3*) and occurs in nature at both low and high temperatures and salinities. It is a shortcut in the nitrogen cycle (see the figure) that was discovered in the early 1990s (*4*). The anammox bacteria, which belong to the group Planctomycetes, contain a membrane-bound organelle in which ammonium and nitrite are converted to nitrogen gas via the toxic and extremely energy-rich hydrazine intermediate. Special lipids found in these bacteria, ladderanes, are believed to assist in keeping the hydrazine within this organelle (*5*). The bacteria use CO_2 as their carbon source for growth and hence do not require organic carbon (*1*). The nitrite required for their growth may be provided by aerobic ammonium-oxidizing bacteria or archaea (*2*). The anammox (I) and nitrification (II) reactions

$$NH_4^+ + NO_2^- \rightarrow N_2 + 2H_2O \quad (I)$$

$$NH_4^+ + 1\tfrac{1}{2}O_2 \rightarrow NO_2^- + 2H^+ + H_2O \quad (II)$$

together yield

$$2NH_4^+ + 1\tfrac{1}{2}O_2 \rightarrow N_2 + 2H^+ + 3H_2O$$

In conventional sewage treatment, organic matter is combusted to carbon dioxide by microorganisms growing in flocs, generally referred to as an "activated sludge." This process requires a lot of electrical energy input

[1]Microbiology, Radboud University Nijmegen, Toernooiveld 1, 6525ED Nijmegen, Netherlands. [2]Biotechnology, Delft University Technology, Julianalaan 67, 2628BC Delft, Netherlands. E-mail: j.g.kuenen@tudelft.nl