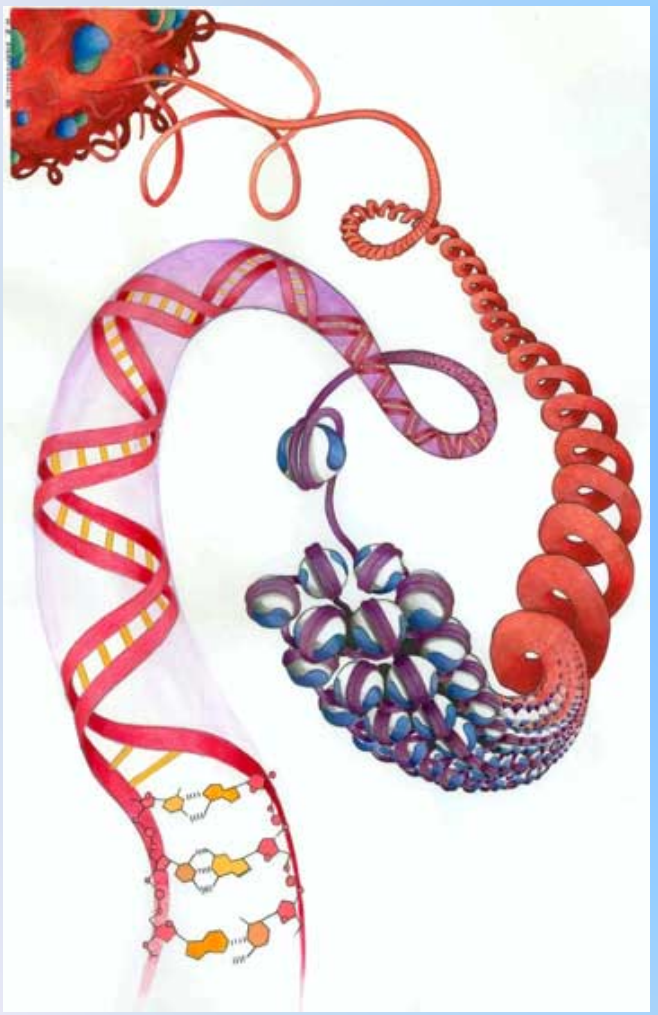
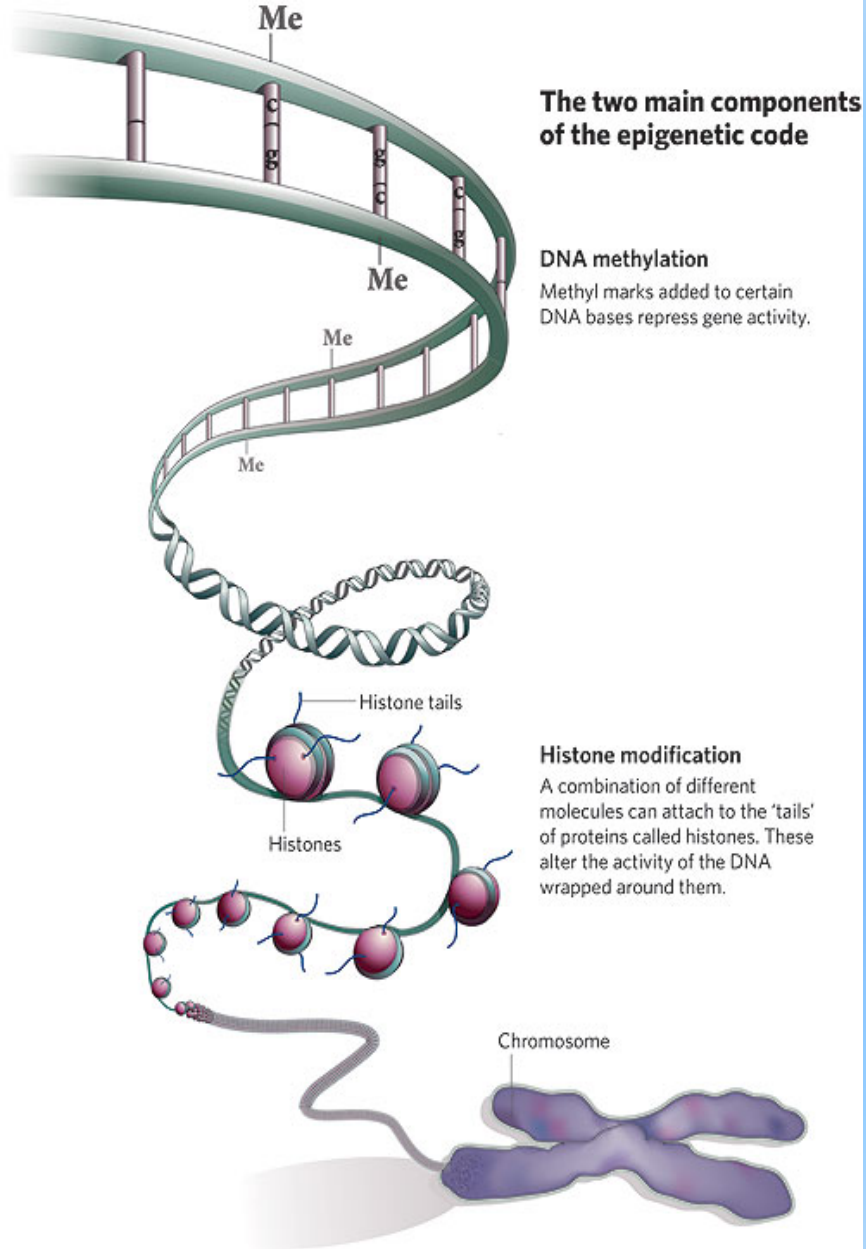
Epigenomics and Aging

How epigenetic regulation of gene expression is related to getting older

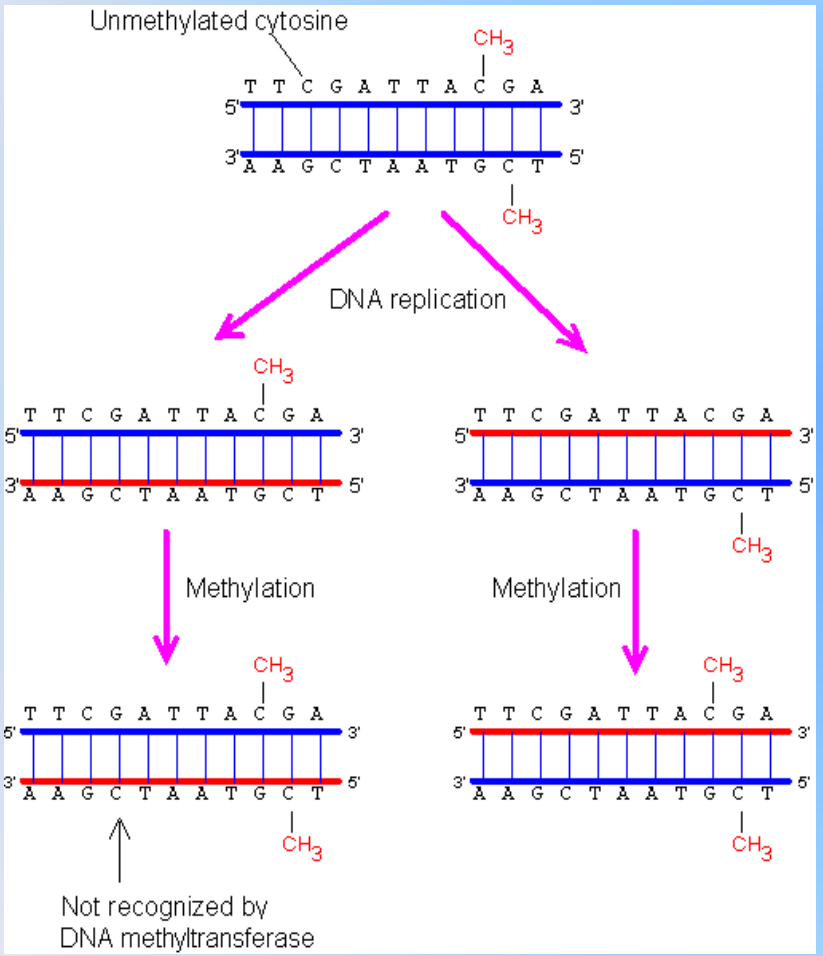




What is epigenomics?

- Study of heritable changes in phenotype or gene expression caused by mechanisms other than changes in DNA sequence.
- Affects which genes are transcribed.
- Reason for cell differentiation
- Main components are DNA methylation and histone modifications.

Methylation



- Addition of a methyl group to the 5 position of cytosine in a cytosine-guanine basepair (CpG)
- Inheritable / passed to cells through replication.
- Suppresses gene expression by
  - 1) physically impeding transcription proteins or
  - 2) recruiting other CpG binding proteins that change histone structure
- Occurs in 60-90% of genes.
- Is not found in "CpG islands" – regions of high unmethylated CpG concentration in promoters of "housekeeping genes"
- Can regulate genes throughout life.

Free Image (Molecular Bio Web Bank)

Histone Modification

- Histones:
  - Act as spools around which DNA winds, allowing DNA to condense into chromatin.
  - Undergo post-translational modifications that regulate genes (ie. Methylation, acetylation, etc.)
- Chromatin:
  - Complex of DNA and histone proteins that make up chromosomes
  - Comes in two varieties:
    - *Heterochromatin* - condensed and generally inactive (unexpressed)
    - *Euchromatin* – uncondensed, transcriptionally active.

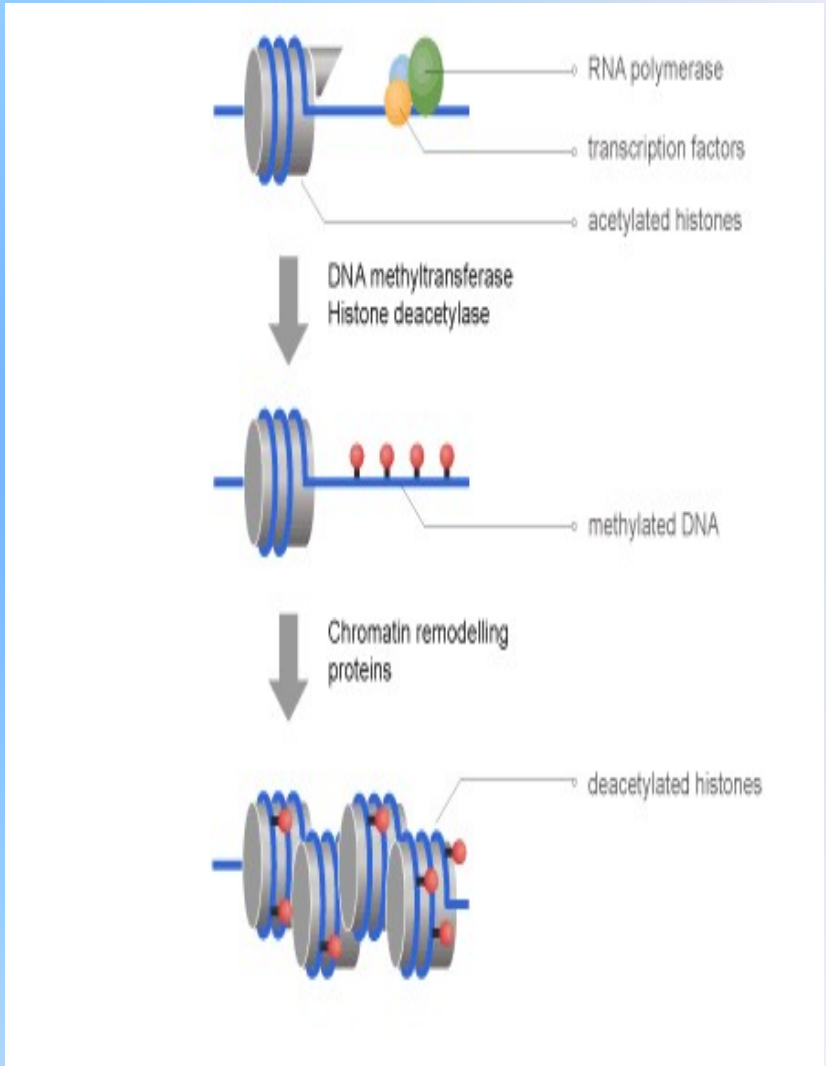
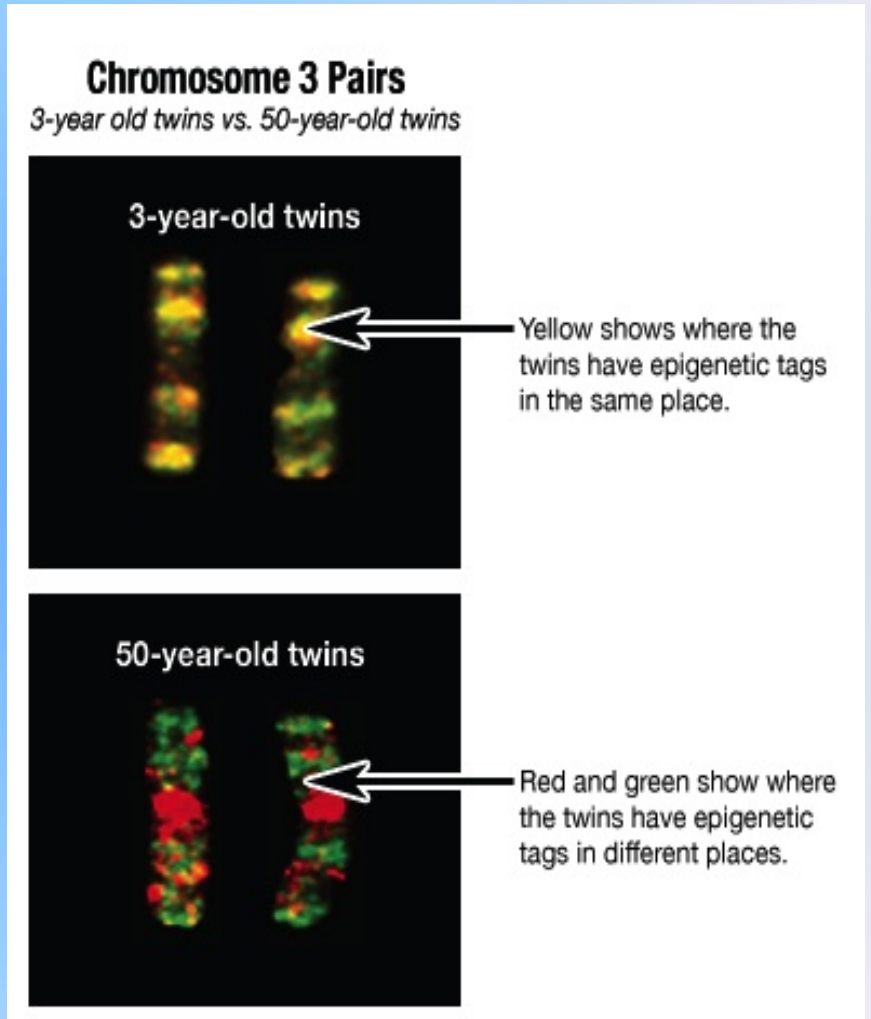


Image borrowed from Richard Twyman, the Wellcome Trust.

Epigenetics Changes over Lifetime

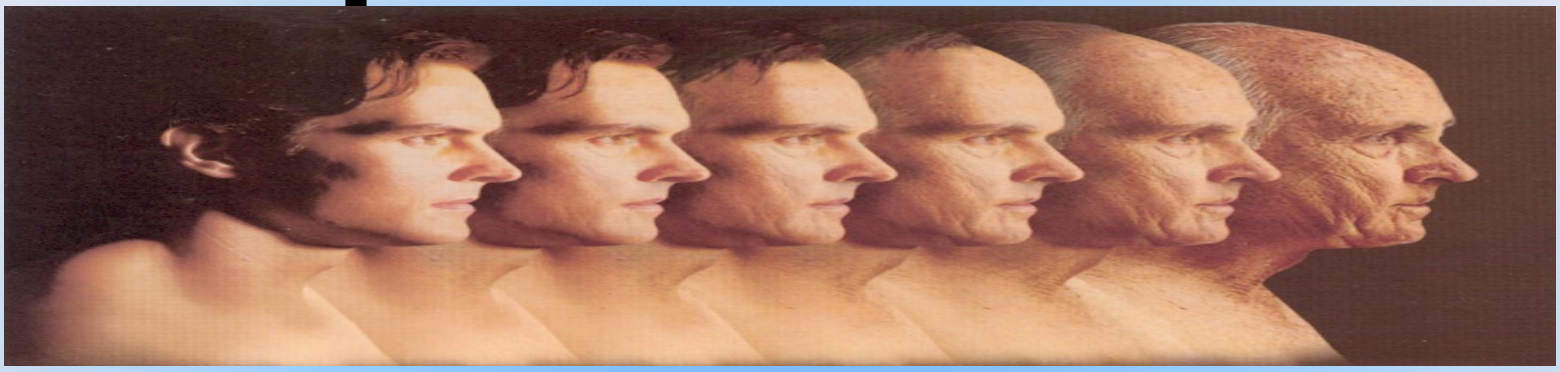
- Monozygotic twins, despite being genetically identical, diverge phenotypically over time
- Overall decrease in methylation as humans age (more genes are "on")
  - Abnormal methylation predominantly occurs at repetitive sequences, meaning herterochromatin are affected most. (inactive genes become active)
- At specific sites, there is a tendency for DNA that was not methylated to become hypermethylated.
  - Occurs in CpG islands, which are regulatory genes.
  - Significant methylation alterations found in:
    - Other epigenetic signalling genes
      - LAMB 1 – involved in subchromosomal domain positioning
      - Genes involved in making enzymes like DNA methyltransferases
    - Telomere maintenance gene loci
      - *TERT*, *ERCC1*, *RAD50*
    - The Werner gene loci – involved in premature aging syndrome
      - Related to DNA maintenance and repair as well as replication



What causes these changes?

- Genetics
  - Familial clustering of methylation changes suggest inheritable methylation stability
- Environmental Exposures
  - Inflammation, carcinogens, and diet are known to cause methylation alterations.
    - Ex: Caloric restriction affects longevity and preproorexin gene expression in mice; Hunger Winter affected the insulin-like growth factor 2 in children.
  - Tobacco, alcohol, arsenic, and asbestos are associated with methylation-induced-gene-inactivation.
    - Hypermethylation of tumor suppressor genes in lung tissue of smokers.
- Random Biological Variability

Consequence 1: Senescence



- **Aging: "the loss of corporal functions accompanied by a general degeneration of cells and tissues"**

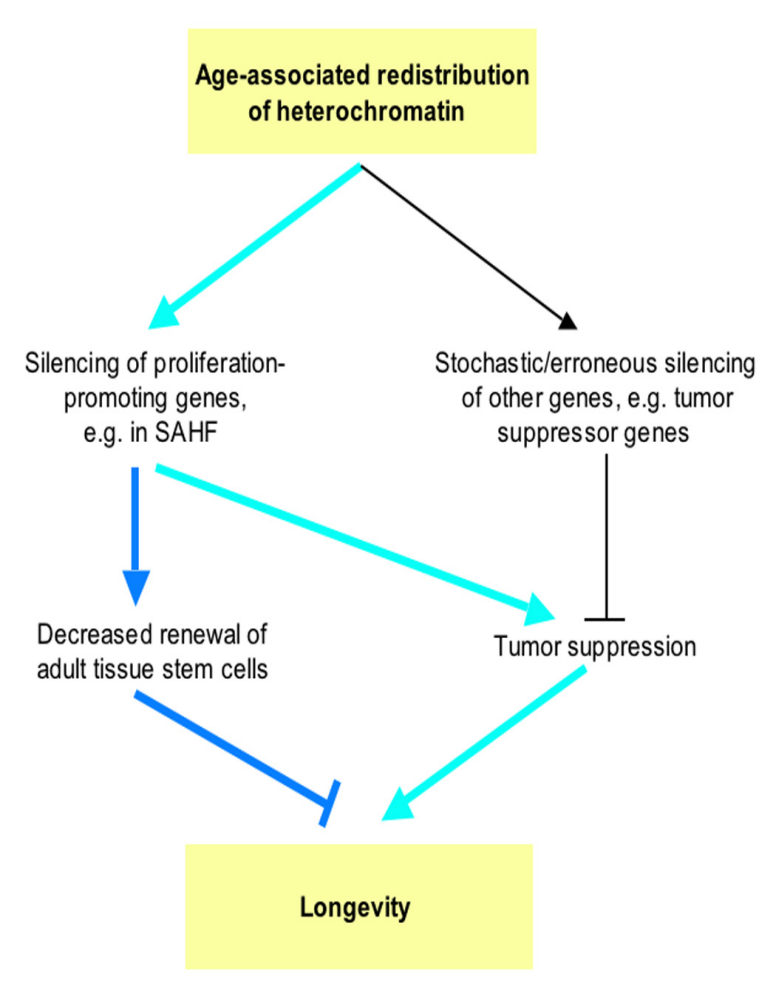
- Accumulated "**chromatin damage**" and cell stress cause increased apoptosis.
- Tissues do not renew themselves as normal because:
  - Decreased DNA methylation and deheterochromatinization contribute to faulty chromosome segregation and age-associated **aneuploidy**.
  - "Senescent" cells become stuck in **proliferation arrest**...
    - Excessive number of cell divisions lead to shortening of telomeres
    - Specialized forms of heterochromatin, called Senescence-Associated-Heterochromain Foci (SAHF), silence expression of proliferation-promoting genes, which contributes to proliferation arrest (ex: baboon skin)
- Leads to gradual deterioration in cell and tissue function with age.
  - ☒ Explains symptoms like cataracts, loss of bone density, loss of muscle mass and strength, wrinkles in skin, etc.

Overall: progressive decay of adult stem cells' potential to maintain tissular homeostasis.

Image from: www.beauty analysis.com

Consequence 2: Disease Susceptibility

- As we age, we become more susceptible to diseases largely due to changes in epigenetics...
- *Cancer*
  - Involves both hypomethylation and hypermethylation
  - **Oncogenes** - prevent apoptosis and instead cause cells to survive and proliferate, causing tumors *(activated)*
  - **Tumor suppressor genes** – promote apoptosis or repression of the cell cyce *(silenced)*
  - Normally, these genes work in conjunction to maintain healthy homeostatis of cells in tissues, but alterations in their normal expression can lead to cancer.
- *Autoimmune diseases*
  - **Autoreactivity genes** – cause cells that react against the organism of which they are part. *(activated)*
  - **Histocompatibility genes** – determine immune "tolerance" to self (silenced)
  - Disruption of gene expression causes immune system to start working against rather than for an organism.



Why haven't we learned?

- *Why haven't people evolved to live longer?*
- Disadvantages of aging occur after reproduction
  - Natural selection could propagate a lethal or harmful gene as long as it appears after reproduction, which is the case in most cancers and chronic diseases.
- "Antagonistic pleiotropy"
  - Some genes cause both increased reproduction in early life and aging in later life, so senescence could be adaptive in evolution.
    - Ex: Follicle depletion in human females causes both more regular cycles in early life and loss of fertility later in life through menopause.

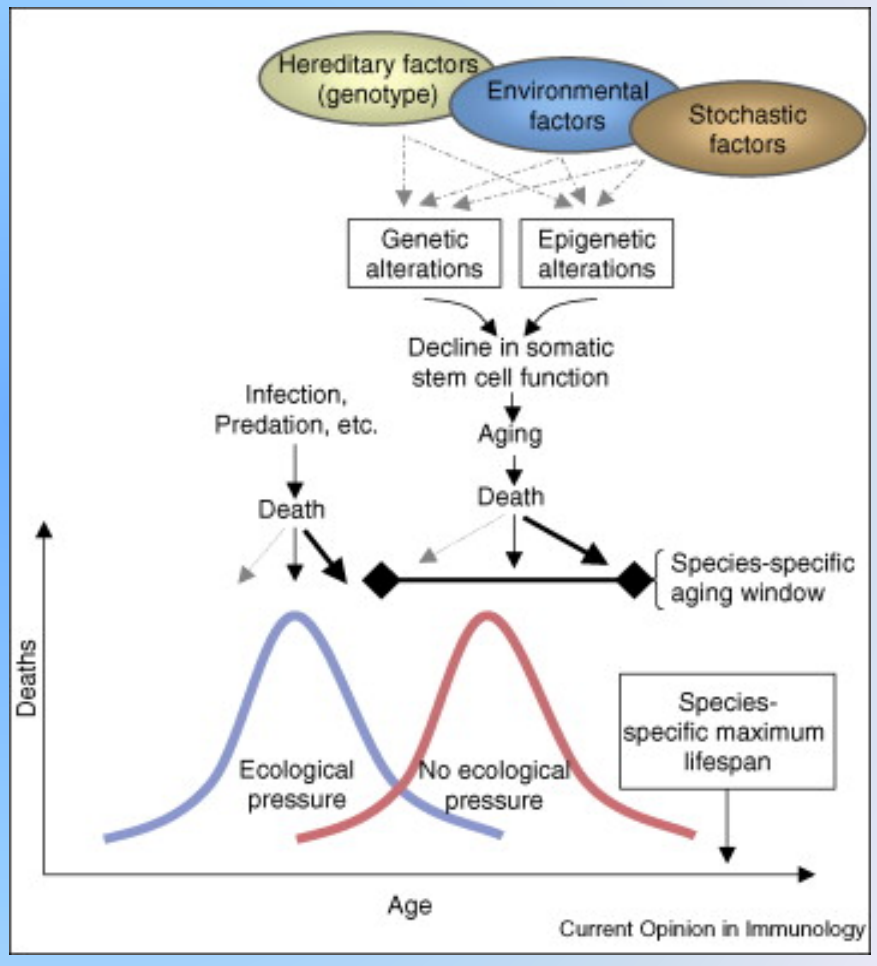
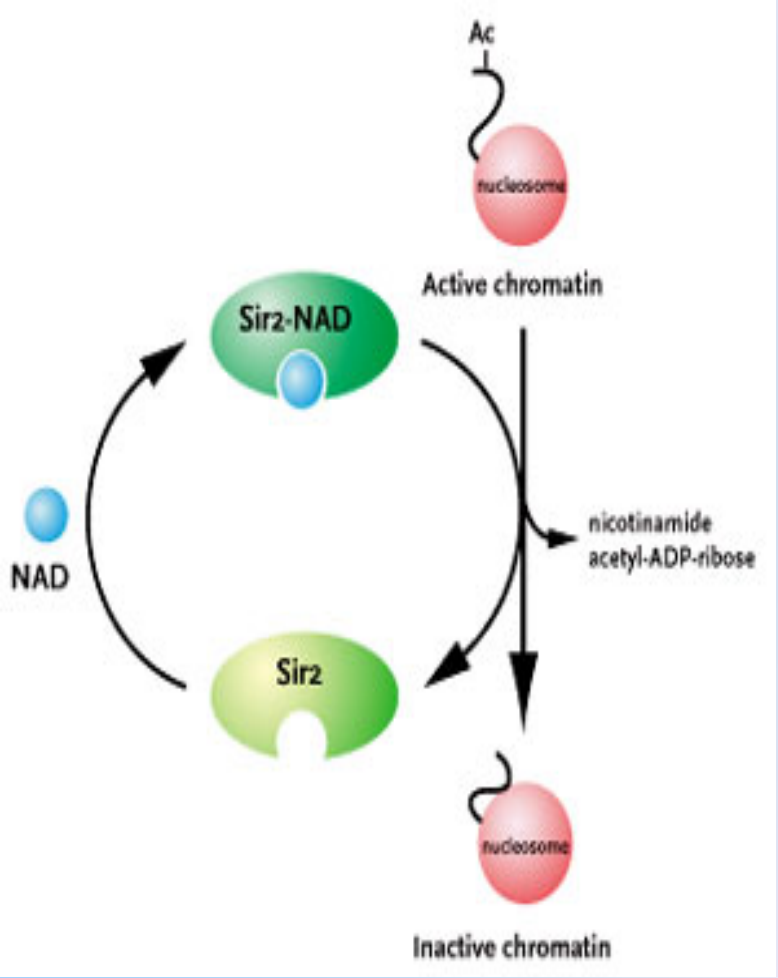


Image by: John Sedivy, Brown University

A more detailed example: Sir2 in Yeast

- In *S. cerevisiae – a type of yeast ,* Sir 2 is an enzyme that removes the acetyl group from histones, with the help of cofactor NAD.
  - Heterochromatinization prevents a sequence of repeats from dividing.
  - This is important, as these repeats are normally prone to recombination to form extrachromosomal rDNA circles (ERCs), which curtail yeast lifespan.
  - By preventing transcription, Sir2 stops these circles from not forming, extending the life cycle of yeast.
- Links cell metabolism, genomic silencing and aging!



The Future...

Unanswered questions:

Which genomic sequences undergo DNA hypermethylation or hypomethylation events in aging cells? Why these?

Is there any particular histone code for an aged cell?

What are the mechanisms by which epigenetic changes occur?

Do the epigenetic phenomena of aging apply in the same manner to all cell types in an organism?

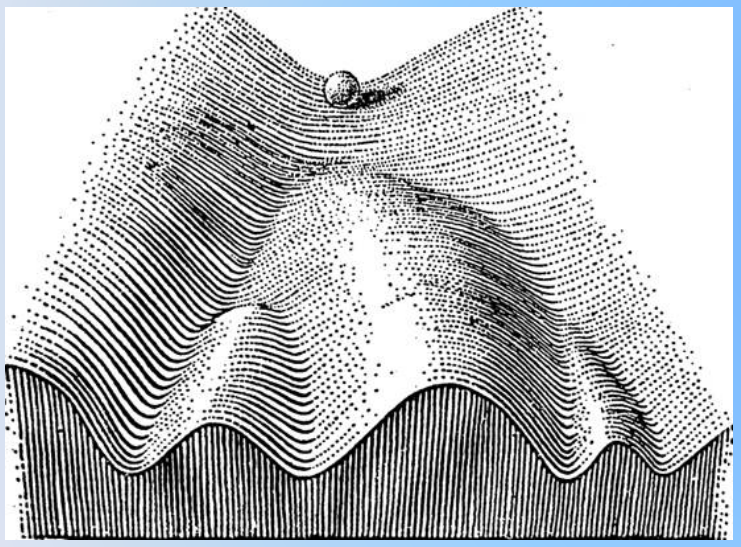
Does a cell deficient in a DNA methylation or histone modifier gene show a characteristic disrupted aging status?

Are there epigenetic drugs that by changing DNA methylation and histone modification patterns could accelerate or slow the aging process?

Scientists hope to develop DNA methylome and a histone modification map that will help to define a 'young' versus an 'old' cell, and to characterize all the chromatin modifier enzymes involved in the process, but first we must understand more thoroughly the molecular basis of aging processes.

Implications for Medicine

"Epigenetics stands at the epicenter of modern medicine because it unites nuclear reprogramming during development, environmentally induced changes on the body, and the ability of cells to respond appropriately to external stimuli."



- *Early diagnosis...*
  - Use age-associated epigenetic alterations as a means of early detection and risk stratification for age-associated diseases
    - High-throughput methods for early detection of cancer based upon age-associated hypermethylation in pre-neoplastic tissue.)
    - Age-associated epigenetic changes in cardiac or immune cells for risk assessment or early detection of cardiovascular disease or declining immune function

Prolonged healthy lives...

- Delay or alleviate some of the most debilitating age-associated diseases

Achievable results...

- Epigenetic alterations are more readily reversible than are genetic alterations. Reversal may be easier than gene therapy.

References:

- Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, et al. (2005) Epigenetic differences arise during the lifetime of monozygotic twins. Proc Natl Acad Sci U S A 102: 10604–10609.
- Kwabi-Addo B, Chung W, Shen L, Ittmann M, Wheeler T, et al. (2007) Age-related DNA methylation changes in normal human prostate tissues. Clin Cancer Res 13: 3796–3802
- Christensen BC, Houseman EA, Marsit CJ, Zheng S, Wrensch MR, et al. (2009) Aging and Environmental Exposures Alter Tissue-Specific DNA Methylation Dependent upon CpG Island Context. PLoS Genet 5(8): e1000602. doi:10.1371/journal.pgen.1000602
- Fraga, Mario F. Genetic and epigenetic regulation of aging. (2009) Department of Immunology and Oncology, National Center for Biotechnology, CNB-CSIC, Cantoblanco, Madrid E-28049, Spain (http://www.sciencedirect.com/science)
- Fraga MF, Esteller M. Trends Genet. Epigenetics and aging: the targets and the marks.(2007) Aug;23(8):413-8. Epub 2007 Jun 7. Review. J Gerontol A Biol Sci Med Sci. 2009 Feb;64(2):195-8. Epub 2009 Feb 27.
- A. Kahn and M.F. Fraga, Epigenetics and aging: status, challenges, and needs for the future, J Gerontol A Biol Sci Med Sci 64 (2009), pp. 195–198.
- John M. Sedivy, Gowrishankar Banumathy, and Peter D. Adams. Aging by epigenetics - a consequence of chromatin damage? (2009) Brown University.
- Schindowski, K., Leutner S, Muller,WE., Eckert A. Age related changes of apoptotic cell death in human lymphocytes. Neurobiol Aging 2000; 21:661-670
- H.T. Bjornsson, M.I. Sigurdsson, M.D. Fallin, R.A. Irizarry, T. Aspelund, H. Cui, W. Yu, M.A. Rongione, T.J. Ekstrom and T.B. Harris et al., Intra-individual change over time in DNA methylation with familial clustering, JAMA 299 (2008), pp. 2877–2883.
- Genetic Science Learning Center, "Identical Twins: Pinpointing Environmental Impact on the Epigenome," Learn.Genetics, 3 December 2009, <http://learn.genetics.utah.edu/content/epigenetics/twins/> (3 December 2009)
- S.-I. Imai, et al., "Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase," Nature, 403:795-800, Feb. 17, 2000.

Morley, John E; Chahla, Elie; Al-Kaade, Saad. Antiaging, longevity and calorie restriction (2009) Lippincott Williams and Wilkins.

Imprint of famine seen in genes of Second World War babies 60 years on. Times Online. October 18, 2008.

- "DNA Methylation", "CpG Islands", "Epigenomics", "Senescence", "Oncogenes", and "Histones", Wikipedia.org