Live Fast, Die Young: The Role of Epigenetics in Stress and Aging

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Outline

1. Psychosocial stress and aging
2. A primer on “epigenesis”
3. Epigenetic mechanisms linking stress and aging
4. Conclusions and future directions
Disclosures

• No conflicts of interest
The global “aging crisis”


Rae et al. Science Translational Medicine 2010
1. Psychosocial stress and aging
„Don‘t stress too much, you will age before your time“

„Every disease results from too much stress; people just try to do much more than they can“
Live Fast, Die Young.

This Chinese man lived for 256 years!
“It was he [Jean Valjean] in fact. The clerk’s lamp illuminated his countenance. He was pale and he trembled slightly. His hair, which had still been gray at his arrival [to the court], was now entirely white; it had turned white during the hour he had sat there.”

Victor Hugo, *Les Misérables*
Stress-related phenotypes increase risk for aging-related disease

Molecular mechanisms?
2. A primer on “epigenesis”
Epigenetics: Historical perspective

- Aristotle (4th century B.C.)
- Lamarck (19th century)
- Waddington (1942)

“Soft inheritance”
“Epigenotype”

21st century
DNA methylation arrays
Methylome-wide sequencing

Discovery of functional DNA methylation
1970s/1980s
The epigenome as molecular interface between the environment and the genome

Meaney & Ferguson-Smith 2010
Epigenetics as a hallmark of aging

- Altered intercellular communication
- Genomic instability
- Stem cell exhaustion
- Telomere attrition
- Cellular senescence
- Mitochondrial dysfunction
- Loss of proteostasis
- Deregulated nutrient-sensing

Lopez-Otin et al. *Cell* 2013
Age-related DNA methylation changes

Epigenetic drift

Epigenetic clock

Associated with aging-related disease phenotypes

Adapted from Jones et al. 2015
How can stress “get under the skin” to impact the epigenome?
Stress and the hypothalamic-pituitary-adrenal axis

Chrousos & Gold 1993; Thomassin et al. 2001
Stress-related phenotypes

Plasma membrane

Cortisol

Cytoplasm

Nucleus

Methylation changes at gene promoters

Demethylation at or near GREs

Histone modifications

Zannas & Chrousos Mol Psychiatry 2017
Stress along the lifespan can shape the epigenome

Global DNA hypermethylation
Local DNA methylation changes
Changes in histone acetylation
Alterations in miRNAs

Global DNA methylation changes
Demethylation of CpGs near GREs
Altered DNA-binding of MeCP2
Changes in histone methylation
Changes in miRNA expression

Changes in DNA methylation
Histone modifications
Altered DNA-binding of MeCP2
Alterations in miRNAs
Chromatin remodeling

Stress exposure

Cumulative stress-induced epigenetic changes

Prenatal life
Childhood
Adolescence
Adulthood
Late-life

Zannas & Chrousos Mol Psychiatry 2017
3. Epigenetic mechanisms linking stress and aging
DNA methylation-based age predictors („epigenetic clocks“)

- Composite predictors combining the status of multiple methylation sites
- \( \text{DNAmAge} = b_0 + b_1 \cdot \text{meth}_1 + b_2 \cdot \text{meth}_2 + \ldots \)
- Can predict age across human tissues (correlation > 90%)
- \( \text{DNAmAge} - \text{Chronological age} = \text{Epigenetic Age Acceleration} = \text{Delta Age} \)

Horvath Genome Biology 2013
Accelerated epigenetic aging as a biomarker for aging-related diseases

- All-cause mortality in late life (Marioni et al. 2015)
- Down syndrome (Horvath et al. 2015)
- Alzheimer’s disease outcomes and pathology (Levine et al. 2015)
- Lung cancer in women (Levine et al. 2015)
- Physical and cognitive decline (Marioni et al. 2015)
- Obesity (Horvath et al. 2014)
- Parkinson’s disease (Horvath & Ritz 2015)
- Cancer, cardiovascular, and all-cause mortality (Perna et al. 2016)
DNA methylation (biological) age

Chronological age

2008

2009

1989
DNA methylation-predicted age strongly correlates with chronological age

Grady (Emory)  
Max Planck cohort

Zannas et al. Genome Biology 2015
Lifetime stress accelerates epigenetic aging in a highly traumatized cohort (Grady)

No effects of recent stress or childhood stress alone

Zannas et al. Genome Biology 2015
Epigenetic clock CpGs tend to be located within glucocorticoid response elements

Expected mean: 48.8 (SD 6.14)
Observed: 85
$p_{\text{perm}} < 0.001$

Zannas et al. Genome Biology 2015
Epigenetic clock CpGs show dynamic methylation changes after dexamethasone

- DNA methylation at baseline and 3hrs after oral dexamethasone
- About one third of epigenetic clock sites show methylation changes (90% demethylated)

Max Planck cohort (n=124)

Adjusted for age, sex, batch effects, depression, and multiple comparisons

Zannas et al. Genome Biology 2015
Gene transcripts neighboring epigenetic clock CpGs are regulated by dexamethasone

- Gene expression before and 3 hours after dexamethasone
- 139/170 genes near clock CpGs show dynamic mRNA changes

Disease enrichment analysis: leukemias, arteriosclerosis, coronary artery disease

Zannas et al. Genome Biology 2015
Summary

• Cumulative lifetime stress, but not recent or child stress alone, accelerate epigenetic aging

• Effects evident only in older ages: ‘wear and tear’ of the epigenome?

• Glucocorticoid signaling may mediate the effects of life stress on the aging epigenome
4. Conclusions and future directions
Conclusions/Future directions

• Stress-related phenotypes influence disease risk through epigenetic modifications
  – Timing/duration/intensity/type?
  – Prevention/reversal by certain interventions?
• Stress-induced epigenetic changes as biomarkers
  – Resilience vs. vulnerability vs. epiphenomena
• Identify novel treatment candidates or even develop epigenetic treatments?
Stress-induced epigenetic changes may be prevented or even reversed

Supportive Family Environments Ameliorate the Link Between Racial Discrimination and Epigenetic Aging: A Replication Across Two Longitudinal Cohorts

Gene H. Brody, Gregory E. Miller, [...], and Edith Chen

Adolescent Stress–Induced Epigenetic Control of Dopaminergic Neurons via Glucocorticoids

Minae Niwa, Hanna Jaaro-Peled, [...], and Akira Sawa

Family-centered prevention ameliorates the longitudinal association between risky family processes and epigenetic aging

Gene H. Brody, Tianyi Yu, Edith Chen, Steven R.H. Beach, and Gregory E. Miller

Lasting Epigenetic Influence of Early-Life Adversity on the BDNF Gene

Tania L. Roth, Farah D. Lubin, Adam J. Funk, J. David Sweatt
Anti-stress/aging interventions?

Relaxation techniques for the epigenome