EPIGENETIC REGULATION OF PAIN: WHAT WE KNOW SO FAR

NIH Pain Consortium Symposium
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SAME GENOME!
EPIGENETICS = “ON OR AROUND” GENOMICS

Genetically identical → Different phenotypes

Different epigenetic modifications leading to different expression patterns
EPIGENETIC REGULATION

Socioeconomic influences
Psychological trauma
Physical injury/trauma
Diet
Exercise
Stress
Hormones
Environmental toxins
Environmental enrichment
Aging

Everything Else

Cancer
Diabetes
Obesity
Cardiovascular
Learning & memory
Neurodegeneration
Psychiatric disorders

Everything Else
EPIGENETIC MECHANISMS

DNA Methylation

Histone modifications

Chromosome

Adapted from Denk and McMahon, Neuron, 2012
HISTONE MODIFICATIONS

HATs = Histone acetyltransferases

HDACs = Histone deacetylases

Adapted from Chuang et al., TINS, 2009
DNA METHYLATION

DNA Methyltransferases (DNMTs)

Methylated DNA binding protein 2 (MeCP2)

Adapted from Szyf and Bick, Child Development 84(1): 49-57, 2012
EPIGENETIC REGULATION OF PAIN

Crow, Denk and McMahon, Genome Med, 2015
EPIGENETIC REGULATION OF PAIN

Risk factors: Genes x Environment

Injury

Chronic Pain: Induction & Maintenance

http://www.afalatino.com/
IMPACT OF MATERNAL CARE

Low licking/grooming
Increased stress response
PUPS

High licking/grooming
Decreased stress response
ADULTS

Early environmental exposure --> persistent behavioural impact in adulthood
MATERNAL CARE & THE GLUCOCORTICOID RECEPTOR (GR)

High licking & grooming

Decreased GR alters the HPA axis and impairs resiliency

Francis et al., Science, 1999
EPIGENETIC CONTROL OF GLUCOCORTICOID RECEPTOR EXPRESSION

Histone Deacetylation (HDACs)
DNA Methylation (DNMTs)

High licking & grooming

Histone Acetylation (HATs)
DNA Demethylation (TETs?)

Low licking & grooming
TRANSLATION TO HUMANS

Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse

Patrick O McGowan¹,², Aya Sasaki¹,², Ana C D’Alessio³, Sergiy Dymov³, Benoit Labonté¹,⁴, Moshe Szyf²,³, Gustavo Turecki¹,⁴ & Michael J Meaney¹,²,⁵

Receptor Expression

% Methylation
IMPLICATIONS FOR PAIN

Socioeconomic factors (e.g. maternal care, abuse)

- Altered physiological response to challenge

Psychosocial risk factors (e.g. resiliency, anxiety)
THE EPIGENOME
MATERNAL REARING: GENOME-WIDE & SYSTEM-WIDE DNA METHYLATION

MR = Maternal Rearing
SPR = Surrogate Rearing

Implications:
- Hundreds of genes
- CNS, periphery, other tissues???
- Peripheral markers for CNS pathology?

Prefrontal Cortex

T-Cells

ASSOCIATION OF TRPA1 METHYLATION IN BLOOD AND HEAT SENSITIVITY IN HUMANS

Differential methylation of the TRPA1 promoter in pain sensitivity

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DISC DEGENERATION & LOW BACK PAIN

SPARC-null mice:

SPARC = Secreted Protein, Acidic, Rich in Cysteine

Progressive, accelerated disc degeneration

Behavioural signs of axial low back pain and radiating leg pain
DISC DEGENERATION IN SPARC-NULL MICE

WT
6 months

SPARC-null
6 months

SPARC-null
18 months

Degenerating Disc

Herniated Disc
DISC DEGENERATION INCREASES WITH AGE

Adapted from Tajerian et al., Mol Pain, 2011
LOW BACK PAIN INCREASES WITH AGE

Adapted from Tajerian et al., Mol Pain, 2011
Hypothesis:

Increased methylation – decreased mRNA
SPARC mRNA AND METHYLATION IN AGING MICE

Adapted from Tajerian et al., Mol Pain, 2011
SPARC METHYLATION IS INCREASED IN PAINFUL HUMAN DISCS

Adapted from Tajerian et al., Mol Pain, 2011
EPIGENETIC REGULATION OF PAIN

Risk factors: Genes x Environment

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Chronic Pain: Induction & Maintenance

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CHRONIC PAIN CHANGES THE BRAIN

Inducible
Long-lasting
Reversible

Does chronic pain change the epigenome?
ALTERED CORTICAL GLOBAL METHYLATION SIX MONTHS POST-NERVE INJURY

Prefrontal Cortex

% Methylation

Control | Injured

0 | 25 | 50 | 75

***
ENVIRONMENTAL ENRICHMENT REVERSES CHRONIC NEUROPATHIC PAIN IN MICE

B. Cold sensitivity

Acetone-evoked behavior (s)

- Neuropathic Enriched
- Sham Enriched
- Neuropathic Impoverished
- Sham Impoverished

Baseline 1 Month 2 Month
ENVIROMENTAL ENRICHMENT ATTENUATES PAIN-RELATED PATHOLOGICAL DEMETHYLATION

Frontal Cortex

% Methylation

**

- Injured
- Control

Environmental Enrichment

Adapted from Tajerian et al., PLOS 2013
THE EPIGENOME
METHYLOME-WIDE ANALYSIS: FRONTAL CORTEX

Sham Control (9 months, rats)

Chronic Neuropathic Pain (9 months, rats)

“..relatively rare… usually obtain this kind of clustering by comparing different tissues, species… “ - Reneau Massart (epigenetics collaborator)

Massart, Gregoire et al., unpublished
METHYLOME-WIDE ANALYSIS: FRONTAL CORTEX

Differentially methylated sites in chronic pain

<table>
<thead>
<tr>
<th>FDR</th>
<th>Differentially methylated probes</th>
<th>Number of genes</th>
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<tbody>
<tr>
<td>&lt;0.01</td>
<td>23,386</td>
<td>3,946</td>
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<tr>
<td>&lt;0.1</td>
<td>44,376</td>
<td>10,483</td>
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<tr>
<td>&lt;0.2</td>
<td>50,189</td>
<td>12,643</td>
</tr>
</tbody>
</table>

Peripheral nerve injury resulted in differential methylation in 1000’s of individual genes

Massart, Gregoire et al., unpublished
DYSREGULATION OF EPIGENETIC MACHINERY

Frontal cortex, nerve injury

DNMT1
$P=0.0006$, $r=0.78$

HDAC1
$P=0.0105$, $r=0.63$

Massart, Gregoire et al., unpublished
DYSREGULATION OF EPIGENETIC MACHINERY

Spinal cord, CFA

Bai et al., Molecular Pain, 2019
Inhibition of class II histone deacetylases in the spinal cord attenuates inflammatory hyperalgesia

Guang Bai, Dong Wei, Shiping Zou, Ke Ren, Ronald Dubner

**Graph:**
- **Y-axis:** Paw withdrawal latency (sec)
- **X-axis:** Baseline, Before i.t., Post i.t.
- **Conditions:** 1 hr CFA, 5 hr CFA, 24 hr CFA
- **Groups:** SAHA i.t., Saline i.t.
- **Significance:** * denotes statistical significance.
HDAC inhibitors attenuate the development of hypersensitivity in models of neuropathic pain

Franziska Denk a,*, Wenlong Huang b, Ben Sidders c, Angela Bithell d, Megan Crow a, John Grist a, Simone Sharma e, Daniel Ziemek f, Andrew S.C. Rice b, Noel J. Buckley d, Stephen B. McMahon a
DYSREGULATION OF PAIN-RELEVANT GENES

Frontal cortex, nerve injury

OPRM1
$P=0.079, \ r=-0.66$

GRIN1
$P=0.0329, \ r=-0.55$

Massart, Gregoire et al., unpublished
DYSREGULATION OF PAIN-RELEVANT GENES

GAD65, HDAC-mediated, nucleus raphe magnus

ARTICLES

Epigenetic suppression of GAD65 expression mediates persistent pain
Zhi Zhang, You-Qing Cai, Fang Zou, Bihua Bie & Zhizhong Z Pan

Sensory neurons, histone acetylation

EPIGENETIC REGULATION OF BDNF EXPRESSION IN THE PRIMARY SENSORY NEURONS AFTER PERIPHERAL NERVE INJURY: IMPLICATIONS IN THE DEVELOPMENT OF NEUROPATHIC PAIN

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Division of Molecular Pharmacology and Neuroscience, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
EPIGENETIC REGULATION OF PAIN: WHAT WE KNOW SO FAR

- Risk factors
- Injury pathology
- Induction and maintenance
- Individual genes
- Genome-wide
- System-wide
- Modulated by environment
- New target identification
- Targeting of epigenetic machinery
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