

EPIGENETICS AND BRAIN. A NEW PARADIGM IN THE STUDY OF BRAIN DISORDERS

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INTRODUCTION

- Epigenetics is a mechanism that regulates gene expression independently of DNA sequence, relying on DNA methylation, histone modifications and RNA interference.
- We could define epigenetic as an instruction book which tells each cell type how to work. Because our genome is identical in each cell type but is the epigenome the one who programs each cell type to operate differently; to increase, downgrade or even silence gene expression.
- Epigenetic molecular mechanisms are emerging as an important component of gene regulation in brain function, including synaptic plasticity, learning and memory, and behavior. Changes in epigenetic markings in response to stimuli induce changes in cellular physiology or behavior.

OBJECTIVE

The aim of this study is to describe the molecular mechanisms involved in the epigenetic changes that occurs in the brain in normal and pathological situations.

ENVIRONMENTAL FACTORS

Maternal care / Parental abuse

Psychological stress
Physical shock

Neglect / isolation /
traumatic experiences

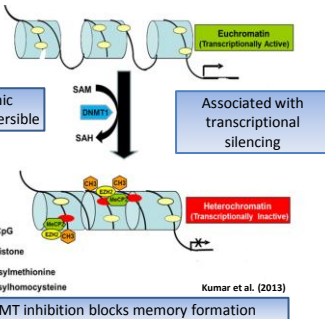
Poor nutrition / toxins /
tobacco / alcohol

EPIGENETIC (RE) PROGRAMMING



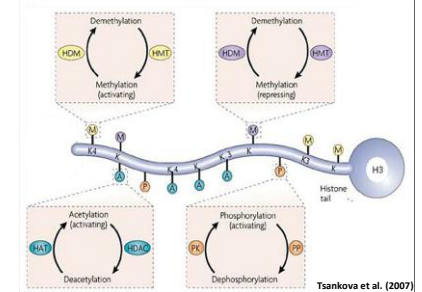
DNA Methylation (DNMTs)

A covalent modification of DNA catalysed by DNA methyltransferases.



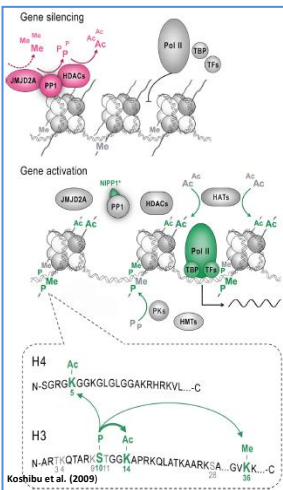
Post-translational histone modifications (PTMs)

Histones are basic proteins that regulate the compaction of the chromatin.

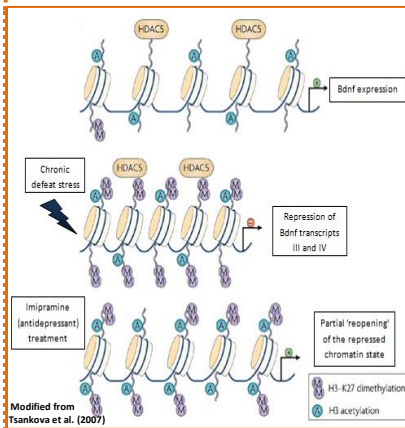


Post-traumatic stress disorder (PTSD)

- Disturbed fear memory → altered epigenetic regulation of gene transcription.
- PP1 → molecular suppressor of memory formation and modulator of fear memory by PTMs.



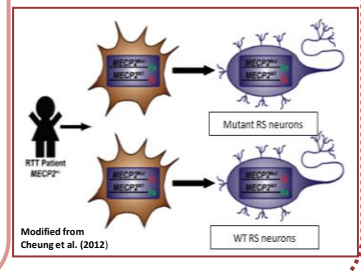
Depression



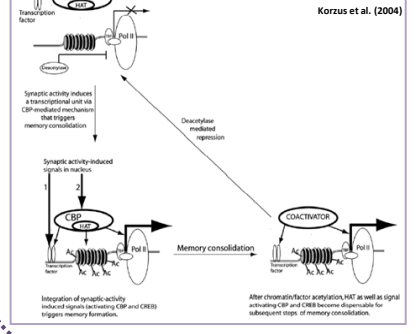
- Chronic stress → depression on susceptible individuals.
- Brain-derived neurotrophic factor (Bdnf) → infused in the hippocampus have antidepressant-like effects in animal models of depression but its lacking give impaired antidepressant responses.
- Chronic imipramine (antidepressant) treatment after defeat stress downregulates Hdac5 expression and increases H3 acetylation.

- Caused by mutations in the X-linked MECP2
- MT → severity of symptoms depend on the ratio of inactivation of paternally X chromosome, in favor of paternal allele (the one mutated) in the more severe clinical phenotype twin.
- DNA methylation status of a number of loci vary between the twins → epigenetic differences, but not genetic differences, are associated with the discordance between these twins.

Rett Syndrome (RS)



Rubinstein-Taybi Syndrome (RTS)



- Mental retardation and skeletal abnormalities → mutations in the gene encoding the CREB-binding protein (CBP)
- CBP → histone acetylation of lysine residues contributing to transcriptional activation.
- Cognitive deficits → related to a reduced level of available CBP to regulate changes in gene expression.

DISCUSSION AND CONCLUSIONS

- Environment plays a pivotal role in the development of various brain diseases by affecting epigenetic marks.
- The brain is one of the most susceptible tissues since epigenetic changes regulate synaptic plasticity, learning and memory and behaviour. That's why alterations on the epigenome could result in the development of brain disorders.
- Adverse antenatal maternal environments, childhood adversity and mental stress cause epigenetic changes in specific brain regions leading to adult brain disorders such as PTSD, depression, RS and RTS.

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