Epigenetic interventions for brain rejuvenation: anchoring age-related transposons

Highlights:
1. Iron and homocysteine accumulation in aging neurons alter genomic methylation.
2. The altered methylome reactivates neuronal cell cycle, enabling transposable element mobilization.
3. miR29/p53 axis restores age-related methylation shifts, reactivating neuronal plasticity.
4. Augmentation of miR-29/p53 axis may preempt neurodegenerative disorder.

Epigenetics refers to the inheritable, non-DNA-related changes in gene expression. Epigenetic mechanisms, including genomic methylation and chromatin condensation, regulate gene transcription and the availability of their products. In general, promoter hypermethylation inhibits, while hypomethylation facilitates adjacent gene expression. With the same token, tight chromatin alignment or heterochromatin inhibits gene transcription, while the looser euchromatin facilitates it.

In contrast to genetic mutations, epigenetic changes are usually reversible, therefore epigenome-modulating therapies may reactivate neuronal plasticity in mature brains (Lennartsson et al., 2015). Furthermore, the recent approval of epigenetic cancer drugs, brought neurodegeneration reversal or delay within reach. Indeed, epi-drugs, including DNA methyltransferase inhibitors (DNMTi), methyl donors and histone deacetylase inhibitors (HDACi) have already entered the clinical practice.

Transposable elements and their anchors: Transposons or transposable elements (TEs) are mobile DNA segments capable of “jumping” from one DNA location to another, increasing the risk of genome destabilization and subsequent neurodegeneration. Indeed, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD) and frontotemporal dementia (FTD) have been associated with TE mobilization. Moreover, excessive TE “awakening” has been reported in schizophrenia, bipolar disorder, autism and drug addictions. On the other hand, correcting age-related methylome alterations in both neurons and glial cells may lower the specific neurodegenerative disorders triggers.

In addition to their mobilization, lower rates of TE methylation was found in AD. Furthermore, TE activation has been connected to the number and function of mitochondria. Indeed, a novel hypothesis links Alu retrotransposon mobilization in aging neurons with mitochondrial dysfunction and neurodegeneration. This TE self-inserts into the regulatory region of Tom40 gene, altering its product, a mitochondrial protein-trafficking channel (Wylie et al., 2016). As protein import is crucial for mitochondrial survival, its disruption may result in mitochondrial loss, an established early marker of neurodegeneration.

TEs are epigenetically anchored during embryogenesis and remain in “epigenetic restraints” throughout the adult life. DNA methylation, the most studied TE anchoring mechanism, refers to the transfer of methyl groups from S-adenosyl methionine (SAM) to the double helix cytosine in a reaction catalyzed by DNA methyltransferases (DNMTs). In this process, SAM is converted to S-adenosylhomocysteine (SAH) and ultimately to homocysteine (HCys). The neurotoxin, HCys, must be rapidly neutralized by remethylation like SSRIs, curcumin downregulates DNMT1, linking this compound to methylation repair (Bartels et al., 2018).

Iron chelators as epi-drugs: Iron chelators, including deferasirox, 8-hydroxyquinolones (8HQ) or PBT 434, were found therapeutic in animal models of neurodegenerative disorders. In addition, several natural compounds have iron chelating properties, including curcumin which also augments p53. Moreover, like SSRIs, curcumin downregulates DNMT1, linking this compound to methylation repair (Bartels et al., 2018).

Iron, as an epi-drug: Iron, a drug which has been used in the treatment of bipolar disorder and depression for several decades, has recently demonstrated therapeutic efficacy in neurodegenerative disorders including AD, PD and ALS.
Figure 1 Age-related methylation changes.
Top: The youthful DNA methylation pattern: promoter hypomethylation enables gene transcription, while transposable elements (TEs) are firmly anchored by hypermethylation. Bottom: Old age methylation: heavy promoter methylation, silencing gene expression, while genome-wide hypomethylation enables neuronal cell cycle reentry and TE mobilization.

From the epigenetic view point, lithium increases global DNA methylation and lowers the methylation of selective promoters, including the brain derived neurotrophic factor (BDNF), enabling its expression. Interestingly, genome-wide hypomethylation and BDNF promoter hypermethylation are the key epigenetic signatures of bipolar disorder. Moreover, lithium inhibits 

Melatonin as an epi-drug: Melatonin is an antioxidant hormone, playing a key role in the regulation of circadian rhythms. At the epigenetic level, melatonin modulates global and promoter methylation. In addition, this hormone upregulates p53, presenting with anti-cancer action. Interestingly, light pollution or excessive night light was demonstrated to destabilize the genome, enabling TE mobilization, probably accounting for the higher incidence of cancer in shift workers. Polyunsaturated fatty acids (PUFAs) as epi-diet: the omega-6/omega-3 ratio: Western diet is characterized by an increase in omega-6 PUFAs and a low intake of omega-3 PUFAs. Impaired omega-6/omega-3 ratio was linked to obesity, neurodegeneration and several psychiatric disorders. The high intake of AA, an omega-6 PUFA, is linked to both iron-induced lipid peroxidation and the upregulation of 12-LOX. On the other hand, omega-3 PUFAs, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are neuroprotective, reducing both iron and HCs.

Folate as an epi-vitamin: Folate is crucial for DNA methylation and HCs remethylation to methionine. Despite its presence in numerous foods and supplements, impaired absorption of folate in elderly is common. One common cause of folate deficiency in seniors is alcohol use. Folate depletion leads to increased vulnerability to genomic damage and neurodegeneration. Indeed, epidemiologic studies have associated low folate levels in seniors with MCI and AD. More studies are needed to assess the role of folate supplementation in neurodegeneration prevention, especially as a large epidemiological study linked low maternal folic acid to autism in offspring. In addition, tumor suppression due to cell cycle arrest was linked to high levels of circulating folate, suggesting p53 augmentation.

Conclusions: Epigenetic changes are reversible, opening exciting opportunities for influencing gene expression and neuronal plasticity by manipulating the environment. Epigenomic markers of aging, global DNA hypomethylation and promoter-specific hypermethylation may be engendered by iron and HCs retention. Since we have discussed extensively the role of iron in beta-amyloid toxicity and TE activation in another review, these subjects were not addressed in detail here (Sfera et al., 2017). However, in the long run, neuronal cell cycle activation and TEs mobilization lead to neurodegeneration. MiR-29/p53 axis may reverse age-related methylation shifts, stabilizing both the genome and the epigenome, therefore removing a major risk factor of neurodegeneration.

Lowering iron and HCs overload can be accomplished via chelation, blood donation and maintaining an adequate omega-6/omega-3 ratio.

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References
Bagott JH, Tamura T (2015) Homosysteme, iron and cardiovascular disease: a hypothesis. Nutrients 7:1108–1118.
Bartels C, Wagner M, Wolfanger S, Ehrenreich H, Schneider A, Alzheimer’s Disease Neuroimaging Initiative (2018) Impact of SSRI therapy on risk of conversion from mild cognitive impairment to Alzheimer’s dementia in individuals with previous depression. Am J Psychiatry 175:232–241.
Devall M, Smith RG, Jeffries A, Hannon E, Davies MN, Schalkwyk L, Mill J, Weedon M, Lunnan K (2017) Regional differences in mitochondrial DNA methylation in human post-mortem brain tissue. Clin Epigenetics 9:47.
Fajardo VA, Fajardo VA, LeBell P, MacPherson REK (2018) Examining the relationship between trace lithium in drinking water and the rising rates of age-adjusted Alzheimer’s disease mortality in Texas. J Alzheimers Dis 61:423–434.
Krumen, IL, Wersto RP, Cardoso-Peixar L, Smilenov L, Chan SL, Christf JF, Emopsk R, Jr., Gioreps M, Mattson MP (2004) Cell cycle activation linked to neuronal cell death initiated by DNA damage. Neuron 41:549–561.
Lennarsson A, Arner E, Fagihomi M, Saxena A, Andersson R, Takahashi H, Nono V, Sug J, Sandelin A, Herash TK, Carinuni P (2015) Remodeling of retrotransposon elements during epigenetic induction of adult visual cortical plasticity by HDAC inhibitors. Epigenetics Chromatin 8:55.
Masutuwa D, Grover A, Delvaux S, Whitehead C, Coleman PD, Rogers J (2010) Epigenetic changes in Alzheimer’s disease: decrements in DNA methylation. Neurobiol Aging 31:2025–2037.
Meadows D, Grover A, Delvaux S, Whitehead C, Coleman PD, Rogers J (2010) Epigenetic changes in Alzheimer’s disease: decrements in DNA methylation. Neurobiol Aging 31:2025–2037.
Pereira PA, Tomas JF, Queiroz JA, Figueiras AR, Sousa F (2016) Recombinant pre-miR-29b for Alzheimer’s disease therapeutics. Sci Rep 6:19946.
Sfera A, Bullock K, Price A, Inderias L, Osorio C (2017) Ferrosenescence: The iron age of neurodegeneration? Mech Ageing Dev doi:10.1016/j.mad.2017.11.012.
Shen X, Chen J, Li J, Koffe J, Herrup K (2016) Neurons in vulnerable regions of the Alzheimer’s disease brain display reduced ATM signaling. eNeuro doi: 10.1523/ENEURO.0124-15.2016.
Sfera A, Fayard L, Osorio C, Price A (2018) Epigenetic interventions for brain rejuvenation: anchoring age-related transposons. Neural Regen Res 13(4):635–636. doi:10.4103/1673-5374.230283.

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Reviewer: Ubaldo Armata, University of Verona Medical School, Italy.
"Comments to authors: I congratulate the author(s) for the clear brevity of their manuscript addressing such complex topics and trying to unify them into a reasonable picture. The main point I wish to address is that their manuscript covers the alterations which old age may induce into the neuronal methylome. Such alterations might advance neurodegenerative diseases and neuronal death. However, I notice that these same alterations are suggested to be involved in several neurodegenerative diseases and not in a single one of them. This implies that the same alterations are likely a part of the old age-linked background which might favor the onset and progression of neurodegenerative diseases yet they are not the specific triggers of diseases as different for instance as AD and Parkinsonism, etc. Specific triggers for each of such diseases are generated. Anyway, improving the old-age related specific methylome changes should reduce the effectiveness of specific triggers of each neurodegenerative disease and this could have a useful clinical impact (see lithium effects, for instance) and entice researchers to address these topics."