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Epigenetics and meditation

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In the last decade, epigenetics has taken center stage to explain the relationships between stress exposure, health and behavior. Acquired or inherited epigenetic changes modulate gene expression states without modifying the DNA sequence itself, they can be long-lasting, yet, they are potentially reversible. Several studies have explored whether meditation-based interventions can influence gene expression profiles towards healthier directions, identifying candidate genes and biological pathways that seem to be sensitive to contemplative practices. However, to date, the clinical implications of these molecular outcomes and their potential long-lasting epigenetic bases remain mostly unknown. The present article addresses these topics from a broad perspective and analyzes future research questions and perspectives at the crossroads of contemplative sciences and epigenetics.

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Introduction

In the beginning of the 20th century, a dominant view in biology was that hereditary substances provided the information necessary to construct an organism. Genocentric ideas strongly influenced the turbulent sociopolitical climate of the time. For example, they were used to justify the approval of a law by the United States Supreme Court in 1927, which permitted compulsory sterilization procedures on human beings to decrease the propagation of undesired traits [e.g. lower cognitive skills, unfitness] 'for the protection and health of the state' [Buck v. Bell, 274 U.S. 200; 1927] [1]. The atrocious human right violations that arose from the eugenic movement had been based on a rhetoric that completely disregarded scientific thinking acknowledging the power of the environment. Back in 1899, the biologist William Morton Wheeler stated that both tendencies, preformationism [heredity and stability] and epigenesis [changes and processes], 'will find their correctives in investigation' [2]. Confirming Wheeler's vision, it is nowadays indisputable that the inherited genetic information is strongly influenced by a broad range of environmental and lifestyle factors [3]. Research over the past years is revealing the complex mechanisms by which cells can become 'structurally modified', even by 'changed habits of body or mind' as Charles Darwin suspected 150 years ago [4]. Environmental factors dynamically generate layers of molecular data that fine-tune the information contained in the genetic code. This epigenetic information [*epi*, from the Greek, means around] stably modulates gene expression without altering the DNA primary structure [5].

Over the last 15 years, numerous studies have associated neurophysiological and behavioral alterations triggered by psychosocial stress with the acquisition of stable epigenetic marks. The inheritability of epigenetic information through cell division in somatic cells seems to explain the enduring effects of environmental exposures at the individual level. Epigenetic mechanisms such as DNA methylation within the hypothalamic-pituitary-adrenal (HPA) axis, changes in the activity of histone deacetylases (HDACs, a family of enzymes that remove acetyl groups from histones and promote gene silencing) and different types of small non-coding RNAs are associated with the development of stress-related psychopathologies in animal models and humans [6–9,10••,11–13].

Epigenetic information can either be inherited or acquired, yet, importantly for biomedical research, it is potentially reversible. Drugs are being actively designed and tested to restore gene activity in diseases caused or aggravated by epigenetic mechanisms [e.g. cancer, inflammation] [14,15]. Similarly, there is increasing evidence on the epigenetic response of pharmacotherapeutic interventions for stress-related disorders [16,17]. However, limited research to date has explored the epigenetic potential of non-pharmacological approaches to improve mental health. Recent encouraging evidence describes changes in DNA methylation profiles in response to cognitive behavior therapy and social support [18,19]. Moreover, findings in rodents suggest that an environmental model which includes cognitive, somatosensorial, motor and visual enrichment may efficiently reduce psychological and behavioral consequences of trauma and stress by removing epigenetic tags and improving adult

neurogenesis and synaptic plasticity [20••,21,22]. In humans, environmental enrichment can be considered inherent to the cultivation of awareness through meditation training, especially at the cognitive and somatosensorial levels. Whether meditation-based interventions [MBIs] could reproduce in humans, some of the epigenetic-based health benefits of the enriched environment model certainly is a thrilling hypothesis.

What is the current knowledge on meditation and epigenetics?

In the last 10 years, several studies have explored the gene expression impact of MBIs in healthy and clinical populations. High throughput screening methodologies [transcriptional microarray techniques and subsequent bioinformatic predictions] have allowed the identification of many candidate genes and biological pathways that seem to be sensitive to contemplative practices [reviewed by Black in this issue, 23]. However, we do not know yet whether the MBI-induced gene expression changes reported to date are generated by epigenetic regulation because they have not been causally associated with any epigenetic mechanism (e.g. specific DNA methylation changes or histone modifications).

Findings in long-term meditators outside periods of formal practice support the hypothesis of underlying long-lasting epigenetic changes acquired through prolonged training. For example, altered transcriptional profiles and differential neurophysiological traits have been detected in long-term meditators compared with meditation-naïve subjects [e.g. Refs. 24–27]. We can also speculate that the epigenetic impact of meditation practice might be dynamic, considering that similar transcriptional and neurophysiological outcomes have been detected after relatively short periods of training [e.g. Refs. 24,28–31]. These intriguing conjectures are starting to be explored. A literature search of original articles using the search terms 'meditation [or mindfulness]' and 'epigenetic' only reveals four pilot studies published till October 2018. Three of these studies analyzed epigenetic profiles in peripheral blood mononuclear cells [PBMCs] in long-term meditators [32–34] and one explored the methylation status of two genes in blood samples from veterans with PTSD after a MBSR intervention [35].

Epigenetic events can be extremely dynamic, as shown in animal models and human peripheral tissues. Indeed, histone modifications and DNA methylation are observed just a few hours after acute stress, nutrient intake, or physical exercise [36–40]. Based on these observations, Kaliman *et al.* [32] explored histone modifications and changes in the expression of chromatin modulatory genes in experienced meditators after a day-long mindfulness retreat (n = 19). The study included a control group with no meditation experience who simultaneously engaged in leisure activities in the same environment (n = 21). Participants in the meditation group had a historical daily meditation practice spanning a minimum of 3 years. After the 8 hours of intervention, meditators showed lower expression levels of several histone deacetylase genes [HDAC2, 3 and 9] and alterations in global modification of histones [H4ac; H3K4me3] in PBMCs compared with controls. The downregulation of HDAC2 predicted a better cortisol recovery after a test of acute psychosocial stress. The meditation group also displayed a downregulation of the proinflammatory gene COX2, which is dependent on HDAC activity. These data may be of clinical interest considering that the pharmacological inhibition of HDACs is currently regarded as a therapeutic avenue for depression [12] and inflammatory-related disorders [41].

Chaix *et al.* [33] did a cross-sectional study comparing DNA methylation profiles in experienced meditators (n = 18) and non-meditators (n = 20), with a specific focus on the epigenetic aging rate (same cohort as in Ref. [32]). In addition to telomere biology [42], specific DNA methylation patterns in the genome accurately predict the rate of cell aging [43]. The level of deviation between the DNA methylation age and the chronological age indicates the rate of epigenetic aging [44,45]. It has been reported that cumulative lifetime stress and trauma accelerate the rhythm of the epigenetic clock [46,47]. Faster ticking epigenetic clocks are associated with several age-related chronic diseases and all-cause mortality risk while slower epigenetic clocks seem to predict longevity as well as better cognitive and physical fitness in the elderly [48••]. Notably, the epigenetic aging rate in meditators significantly decreased with the number of years of formal practice, which suggests that integrating meditation into a daily routine may have increasing protective effects on the epigenetic aging rate, with potential health benefits in the long run.

Using a similar technology (Illumina Infinium HumanMethylation450 BeadChip), Garcia-Campayo *et al.* [34] compared the methylome of meditators with more than 10 years of experience (n = 17) with a control group of meditation-naïve subjects (n = 17). This study found 64 differentially methylated regions (DMRs) in meditators versus controls, which corresponded to 43 genes, most of them linked to neurological and psychiatric disorders, cardiovascular disease and cancer. Bioinformatic analysis of the methylation data suggested that DMRs were involved in the cellular response to unfolded protein, neurotransmission, lipid metabolism and glucose homeostasis. *In silico* analysis also predicted that the epigenetic response to mindfulness practice may modulate inflammatory pathways dependent on tumor necrosis factor alpha and NF-κB signaling, which further supports the potential of MBIs in the treatment of chronic inflammatory conditions.

Bishop *et al.* [35] analyzed genomic DNA isolated from peripheral blood samples from veterans with long-standing PTSD. Participants were classified as responders or non-responders to a MBSR program which included PTSD psychoeducation, based on PTSD symptom severity reduction post-MBSR (n = 11/group). To identify potential biomarkers, the authors explored the methylation status of CpG sites in regions of two genes, the depression-associated serotonin transporter (SLC6A4) and HPA-related FK506 binding protein 5 (FKBP5). Percent methylation differences were evaluated pre-MBSR and post-MBSR in both groups. While no changes were detected in the methylation status of the SLC6A4 gene, after the intervention, responders had a decrease and non-responders had an increase in the methylation of FKBP5 intron 7, which contains a glucocorticoid response element. This study suggests that the methylation of the FKBP5 gene may be a biomarker of response to MBSR in PTSD and provides relevant information on the molecular mechanisms triggered by mindfulness training.

Considerations for future mindfulness research involving epigenetic analysis

Research in the area of epigenetics and meditation, while exciting, is still in its infancy. Researchers in epigenetics are faced with the challenge of selecting among rapidly evolving technologies and methods for data analysis. The fact that epigenetic profiles can be significantly influenced over short periods of time by environmental exposures and lifestyle needs to be taken into account for the data collection and modeling. The discussion of these topics is beyond the scope of this article, but other authors have provided guidelines to select accurate tools for gene-specific and genome wide DNA methylation analysis [e.g. Ref. 49].

Longitudinal randomized and controlled trials involving larger samples are required to identify and validate specific epigenetic events triggered by MBIs and, most importantly, to characterize the actual effectiveness of such molecular changes in improving well-being and health care. Predictions of cellular signalling pathways and functional networks through bioinformatic analysis based on high throughput data is an integral part of molecular research. This type of analysis is often presented as main results in meditation studies involving molecular characterization. However, it is critical to consider that the pattern and level of epigenetic marks and gene expression usually differ across different cell types and tissues. Changes detected in accessible biological samples (e.g. saliva, blood or skin cells) may not reflect the status in other tissues and organs. Although computational-based methods are good starting points in biomedical research, experimental validation of *in silico*-derived data is required. Therefore, future molecular studies aimed at connecting MBIs with long-term health and disease will need to validate bioinformatic predictions by exploring associations of gene expression and epigenetic changes with precise neurophysiological outcomes in healthy subjects and clinical conditions.

Meditation for next generations?

In 1868, Charles Darwin wrote: "On any ordinary view, it is unintelligible how changed conditions, whether acting on the embryo, the young or adult, can cause inherited modifications. It is equally or even more unintelligible on any ordinary view, how the effects of the long-continued use or disuse of any part, or of changed habits of body or mind, can be inherited. A more perplexing problem can hardly be proposed; but on our view we have only to suppose that certain cells become at last structurally modified . . . " [4]. Since then, studies in plants, animal models and humans have provided evidence for the transmission of epigenetic information across generations with developmental, health and potential evolutionary implications [50,51,52••,53]. Research in animal models and human epidemiological data suggests that epigenetic information acquired through parental experiences, including preconceptional maternal or paternal stress, may account for the susceptibility of the offspring to certain diseases, brain alterations, development of psychopathologies and maladaptive behaviors [54,55••]. These and many other findings highlight the need to sensitize medicine and policymakers about the potential multigenerational impact of stress. The potential reversibility of epigentic information and the possibility of modulating the epigenome towards healthier states across generations are critical topics for future research on epigenetics and well-being.

Questions for future research

Our limited experimental evidence on meditation and epigenetics needs to be expanded in the coming years addressing some fundamental questions. Can meditation induce long-lasting epigenetic events related to disease prevention and healthy aging? Can MBIs help prevent or counterbalance the epigenetic dimension of trauma and stress exposure? What are the sensitive periods for this? Could the practice of meditation modify the epigenome of the germ cells [oocytes or sperm], suggesting a potential for transmission of acquired information to subsequent generations? Research at the crossroads of meditation and epigenetics will hopefully provide mechanistic insight into effective and long-lasting non-pharmacological strategies to improve well-being and health and may offer a molecular perspective to interconnectedness, a key teaching of contemplative traditions.

Conflict of interest statement

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest

1. Reilly PR: **Eugenics and involuntary sterilization: 1907-2015**. *Annu Rev Genomics Hum Genet* 2015, **16**:351-368.

2. Wheeler WM: *Caspar Friedrich Wolff and the Theoria Generationis*. Woods Hole: Biol Lectures Marine Biol Lab; 1899, 265-284.

3. Párrizas M, Gasa R, Kaliman P: **Epigenetics of lifestyle: the plasticity of the genetic information**. *Epigenetics of Lifestyle*. Bentham eBooks; 2012:3-35 http://dx.doi.org/10.2174/9781608052998112010l: eISBN: 978-1-60805-299-8.

4. Darwin C: **Of pangenesis**. *The Variation of Animals and Plants under Domestication* 1868, **vol. II** (Chapter XXVII). ISBN-13: 978-0801858673, ISBN-10: 0801858674.

5. Berger SL, Kouzarides T, Shiekhattar R, Shilatifard A: **An operational definition of epigenetics**. *Genes Dev* 2009, **23**:781-783.

6. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ: **Epigenetic programming by maternal behavior**. *Nat Neurosci* 2004, **7**:847-854.

7. Hu Z, Jiang Y, Huo X, Yang Y, Davies H, Botchway BOA, Fang M: **Prospective role of microRNAs in depression**. *Curr Med Chem* 2017, **24**:3508-3521.

8. Turecki G, Meaney MJ: **Effects of the social environment and stress on glucocorticoid receptor gene methylation: a systematic review**. *Biol Psychiatry* 2016, **79**:87-96.

9. Essex MJ, Boyce WT, Hertzman C, Lam LL, Armstrong JM, Neumann SM, Kobor MS: **Epigenetic vestiges of early developmental adversity: childhood stress exposure and DNA methylation in adolescence**. *Child Dev* 2013, **84**:58-75.

10. •• Argentieri MA, Nagarajan S, Seddighzadeh B, Baccarelli AA, Shields AE: **Epigenetic pathways in human disease: the impact of DNA methylation on stress-related pathogenesis and current challenges in biomarker development**. *EBioMedicine* 2017, **18**:327-350.
Valuable contribution in providing a review of the clinical associations that have been reported in relation to the physiological impact of social and environmental stress and DNA methylation sites potentially meaningful as prognostic biomarkers.

11. Tyrka AR, Ridout KK, Parade SH: **Childhood adversity and epigenetic regulation of glucocorticoid signaling genes: associations in children and adults**. *Dev Psychopathol* 2016, **28**:1319-1331.

12. Misztak P, Pańczyszyn-Trzewik P, Sowa-Kućma M: **Histone deacetylases (HDACs) as therapeutic target for depressive disorders**. *Pharmacol Rep* 2018, **70**:398-408.

13. Yuan H, Mischoulon D, Fava M, Otto MW: **Circulating microRNAs as biomarkers for depression: many candidates, few finalists**. *J Affect Disord* 2018, **233**:68-78.

14. Cao F, Zwinderman MRH, Dekker FJ: **The process and strategy for developing selective histone deacetylase 3 inhibitors**. *Molecule* 2018, **23**.

15. Agrawal K, Das V, Vyas P, Hajdúch M: **Nucleosidic DNA demethylating epigenetic drugs - a comprehensive review from discovery to clinic**. *Pharmacol Ther* 2018, **188**:45-79.

16. Schiele MA, Domschke K: **Epigenetics at the crossroads between genes, environment and resilience in anxiety disorders**. *Genes Brain Behav* 2018, **17**:e12423.

17. Ziegler C, Schiele MA, Domschke K: **Patho- and therapyepigenetics of mental disorders**. *Nervenarzt* 2018, **89 (11)**:1303-1314 http://dx.doi.org/10.1007/s00115-018-0625-y.

18. Roberts S, Keers R, Lester KJ, Coleman JR, Breen G, Arendt K, Blatter-Meunier J, Cooper P, Creswell C, Fjermestad K *et al.*: **HPA axis related genes and response to psychological therapies: genetics and epigenetics**. *Depress Anxiety* 2015, **32**:861-870.

19. Brody GH, Yu T, Chen E, Beach SR, Miller GE: **Family-centered prevention ameliorates the longitudinal association between risky family processes and epigenetic aging**. *J Child Psychol Psychiatry* 2016, **57**:566-574.

20. •• Gapp K, Bohacek J, Grossmann J, Brunner AM, Manuella F, Nanni P, Mansuy IM: **Potential of environmental enrichment to prevent transgenerational effects of paternal trauma**. *Neuropsychopharmacology* 2016, **41**:2749-2758.
This paper shows the transgenerational transmission of behavioral and epigenetic alterations in response to paternal early life stress and how this is prevented by preconceptional paternal environmental enrichment (EE).

21. McCreary JK, Erickson ZT, Hao Y, Ilnytskyy Y, Kovalchuk I, Metz GA: **Environmental intervention as a therapy for adverse programming by ancestral stress**. *Sci Rep* 2016, **6**:37814.

22. Nithianantharajah J, Hannan AJ: **Enriched environments, experience-dependent plasticity and disorders of the nervous system**. *Nat Rev Neurosci* 2006, **7**:697-709.

23. Black, DS, Christodoulou, G, Cole S. A molecular perspective on the health impact of mindfulness training: a mind-body conceptual framework, *Current Opinion in Psychology*, special issue Mindfulness, in press.

24. Dusek JA, Otu HH, Wohlhueter AL, Bhasin M, Zerbini LF, Joseph MG, Benson H, Libermann TA: **Genomic counter-stress changes induced by the relaxation response**. *PLoS One* 2008, **3**:e2576.

25. Ferrarelli F, Smith R, Dentico D, Riedner BA, Zennig C, Benca RM, Lutz A, Davidson RJ, Tononi G: **Experienced mindfulness meditators exhibit higher parietal-occipital EEG gamma activity during NREM sleep**. *PLoS One* 2013, **8**:e73417.

26. Lazar SW, Kerr CE, Wasserman RH, Gray JR, Greve DN, Treadway MT, McGarvey M, Quinn BT, Dusek JA, Benson H *et al.*: **Meditation experience is associated with increased cortical thickness**. *Neuroreport* 2005, **16**:1893-1897.

27. Chételat G, Mézenge F, Tomadesso C, Landeau B, Arenaza-Urquijo E, Rauchs G, André C, de Flores R, Egret S, Gonneaud J *et al.*: **Reduced age-associated brain changes in expert meditators: a multimodal neuroimaging pilot study**. *Sci Rep* 2017, **7**:10160.

28. Dentico D, Ferrarelli F, Riedner BA, Smith R, Zennig C, Lutz A, Tononi G, Davidson RJ: **Short meditation trainings enhance non-REM sleep low-frequency oscillations**. *PLoS One* 2016, **11**: e0148961.

29. Acevedo BP, Pospos S, Lavretsky H: **The neural mechanisms of meditative practices: novel approaches for healthy aging**. *Curr Behav Neurosci Rep* 2016, **3**:328-339.

30. Kurth F, Cherbuin N, Luders E: **Promising links between meditation and reduced (brain) aging: an attempt to bridge some gaps between the alleged fountain of youth and the youth of the field**. *Front Psychol* 2017, **8**:860.

31. Bhasin MK, Dusek JA, Chang BH, Joseph MG, Denninger JW, Fricchione GL, Benson H, Libermann TA: **Relaxation response induces temporal transcriptome changes in energy metabolism, insulin secretion and inflammatory pathways**. *PLoS One* 2013, **8**:e62817.

32. Kaliman P, Alvarez-López MJ, Cosín-Tomás M, Rosenkranz MA, Lutz A, Davidson RJ: **Rapid changes in histone deacetylases and inflammatory gene expression in expert meditators**. *Psychoneuroendocrinology* 2014, **40**:96-107.

33. Chaix R, Alvarez-López MJ, Fagny M, Lemee L, Regnault B, Davidson RJ, Lutz A, Kaliman P: **Epigenetic clock analysis in long-term meditators**. *Psychoneuroendocrinology* 2017, **85**:210-214.

34. García-Campayo J, Puebla-Guedea M, Labarga A, Urdanoz A, Roldan M, Martinez de Morentin X, Perdones-Montero A, Montero-Marin J, Mendioroz M: **Epigenetic response to mindfulness in peripheral blood leukocytes involves genes linked to common human diseases**. *Mindfulness* 2018, **9**:1146.

35. Bishop JR, Lee AM, Mills LJ, Thuras PD, Eum S, Clancy D, Erbes CR, Polusny MA, Lamberty GJ, Lim KO: **Methylation of**

FKBP5 and SLC6A4 in relation to treatment response to mindfulness based stress reduction for posttraumatic stress disorder. *Front Psychiatry* 2018, **9**:418.

36. Papale LA, Li S, Madrid A, Zhang Q, Chen L, Chopra P, Jin P, Keleş S, Alisch RS: **Sex-specific hippocampal 5-hydroxymethylcytosine is disrupted in response to acute stress**. *Neurobiol Dis* 2016, **96**:54-66.

37. Rodrigues GM Jr, Toffoli LV, Manfredo MH, Francis-Oliveira J, Silva AS, Raquel HA, Martins-Pinge MC, Moreira EG, Fernandes KB, Pelosi GG, Gomes MV: **Acute stress affects the global DNA methylation profile in rat brain: modulation by physical exercise**. *Behav Brain Res* 2015, **279**:123-128.

38. Chandramohan Y, Droste SK, Arthur JS, Reul JM: **The forced swimming-induced behavioural immobility response involves histone H3 phospho-acetylation and c-Fos induction in dentate gyrus granule neurons via activation of the N-methyl-D-aspartate/extracellular signal-regulated kinase/mitogen- and stress-activated kinase signalling pathway**. *Eur J Neurosci* 2008, **27**:2701-2713.

39. Barrès R, Yan J, Egan B, Treebak JT, Rasmussen M, Fritz T, Caidahl K, Krook A, O'Gorman DJ, Zierath JR: **Acute exercise remodels promoter methylation in human skeletal muscle**. *Cell Metab* 2012, **15**:405-411.

40. Myzak MC, Tong P, Dashwood WM, Dashwood RH, Ho E: **Sulforaphane retards the growth of human PC-3 xenografts and inhibits HDAC activity in human subjects**. *Exp Biol Med (Maywood)* 2007, **232**:227-234.

41. Sweet MJ, Shakespear MR, Kamal NA, Fairlie DP: **HDAC inhibitors: modulating leukocyte differentiation, survival, proliferation and inflammation**. *Immunol Cell Biol* 2012, **90**:14-22.

42. Blackburn EH, Epel ES, Lin J: **Human telomere biology: a contributory and interactive factor in aging, disease risks, and protection**. *Science* 2015, **350**:1193-1198.

43. Horvath S: **DNA methylation age of human tissues and cell types**. *Genome Biol* 2013, **14**:R115.

44. Hannum G, Guinney J, Zhao L, Zhang L, Hughes G, Sadda S, Klotzle B, Bibikova M, Fan JB, Gao Y *et al.*: **Genome-wide methylation profiles reveal quantitative views of human aging rates**. *Mol Cell* 2013, **49**:359-367.

45. Chen BH, Marioni RE, Colicino E, Peters MJ, Ward-Caviness CK, Tsai PC, Roetker NS, Just AC, Demerath EW, Guan W *et al.*: **DNA methylation-based measures of biological age: meta-analysis predicting time to death**. *Aging (Albany NY)* 2016, **8**:1844-1865.

46. Zannas AS, Arloth J, Carrillo-Roa T, Iurato S, Röh S, Ressler KJ, Nemeroff CB, Smith AK, Bradley B, Heim C *et al.*: **Lifetime stress accelerates epigenetic aging in an urban, African American cohort: relevance of glucocorticoid signaling**. *Genome Biol* 2015, **16**:266.

47. Boks MP, van Mierlo HC, Rutten BP, Radstake TR, De Witte L, Geuze E, Horvath S, Schalkwyk LC, Vinkers CH, Broen JC, Vermetten E: **Longitudinal changes of telomere length and epigenetic age related to traumatic stress and post-traumatic stress disorder**. *Psychoneuroendocrinology* 2015, **51**:506-512.

48. •• Horvath S, Raj K: **DNA methylation-based biomarkers and the epigenetic clock theory of ageing**. *Nat Rev Genet* 2018, **19**:371-384.
Valuable contribution in discussing how accelerated epigenetic age predicts several age-related phenotypes.

49. Chatterjee A, Rodger EJ, Morison IM, Eccles MR, Stockwell PA: **Tools and strategies for analysis of genome-wide and gene-specific DNA methylation patterns**. *Methods Mol Biol* 2017, **1537**:249-277.

50. Lämke J, Bäurle I: **Epigenetic and chromatin-basnmental stress adaptation and stress memory in plants**. *Genome Biol* 2017, **18**:124.

51. Radford EJ: **Exploring the extent and scope of epigenetic inheritance**. *Nat Rev Endocrinol* 2018, **14**:345-355.

52. •• Horsthemke B: **A critical view on transgenerational epigenetic inheritance in humans**. *Nat Commun* 2018, **9**:2973.
Valuable contribution in discussing why, while the transmission of epigenetic information through the germline is well accepted in many species, its occurrence in mammals and humans remains for some scientists a topic of controversial debate.

53. Skinner MK: **Environmental epigenetics and a unified theory of the molecular aspects of evolution: a neo-Lamarckian concept that facilitates neo-Darwinian evolution**. *Genome Biol Evol* 2015, **7**:1296-1302.

54. Yehuda R, Meaney MJ: **Relevance of psychological symptoms in pregnancy to intergenerational effects of preconception trauma**. *Biol Psychiatry* 2018, **83**:94-96.

55. •• Bowers ME, Yehuda R: **Intergenerational transmission of stress in humans**. *Neuropsychopharmacology* 2016, **41**:232-244.
Valuable contribution in discussing how the intergenerational transmission of preconceptional parental trauma or exposure to stress is currently supported by results from cohorts of Holocaust survivor offspring, subjects prenatally exposed to nuclear and natural disaster, and other populations.