Title
Challenging dogmas: How transgenerational epigenetics reshapes our views on life

Journal
Journal of Experimental Zoology Part A Ecological and Integrative Physiology, 337(1)

ISSN
2471-5638

Authors
Wang, Harrison D
Allard, Patrick

Publication Date
2022

DOI
10.1002/jez.2465

Peer reviewed

HHS Public Access

Author manuscript

J Exp Zool A Ecol Integr Physiol. Author manuscript; available in PMC 2023 January 01.

Published in final edited form as:

J Exp Zool A Ecol Integr Physiol. 2022 January ; 337(1): 70–74. doi:10.1002/jez.2465.

Challenging dogmas: how transgenerational epigenetics reshapes our views on life.

Harrison D. Wang[1], **Patrick Allard**[1,2]

[1.]The Institute for Society and Genetics, University of California, Los Angeles, Los Angeles, California. USA

[2.]Molecular Biology Institute, University of Los Angeles, California. Los Angeles, California. USA

Abstract

The emergence of the field of Transgenerational Epigenetics Inheritance (TEI) has profoundly reshaped our understanding of the relationships between environment, soma, and germ cells as well as of heredity. TEI refers to the changes in chromatin state, gene expression, and/or phenotypes that are transmitted across several generations without involving changes to the DNA sequences. TEI has direct connections with, and feeds from, the fields of molecular biology, genetics, developmental biology, and reproductive biology, among others. However, the expansion of TEI-related research, has profoundly reshaped boundaries within each field and often led to the erosion of theories and concepts considered as tenets of biology. We first explore how the molecularization of biology has shifted the definition of epigenetics to include the notion of heredity and how epigenetics has refined our understanding of the central dogma of biology. The demonstrated transfer of environmental information from soma to germ cell through extra-cellular vesicles and subsequent alteration of health outcomes in offspring has put a definite end to the long-held principle of the Weismann barrier. TEI has also simultaneously led to the revival of the inheritance of acquired characteristics while further eroding the concept of an epigenetic “blank slate” in mammals. Using an historical framework, and *via* the exploration of central studies in the field, in this perspective article, we will draw a compelling argument for the revolutionary aspect of TEI in biology.

Graphical Abstract

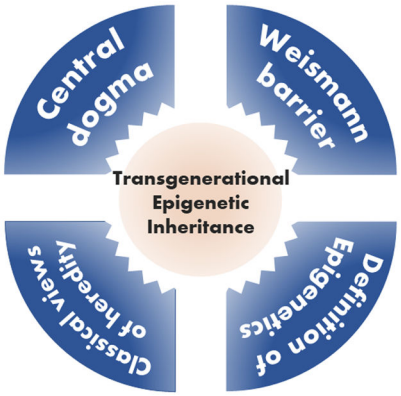
Corresponding author: Patrick Allard, 621 Charles E. Young Drive S., Life Science Building 3360, University of California, Los Angeles, Los Angeles, 90095. pallard@ucla.edu.

Conflict of interest

The authors declare no conflict of interest.

Data availability

No dataset is associated with this publication.



Keywords

transgenerational inheritance; TEI; epigenetics

I. Introduction

Transgenerational Epigenetics Inheritance (TEI) can be defined as changes in chromatin state, gene expression, and/or phenotypes that are transmitted across several generations without involving changes to the DNA sequences. This subfield of epigenetics has grown tremendously in the last decade due to major findings in a variety of model systems that have helped reshape the molecular understanding of heredity. As we will argue, TEI has also been able to find its place as a field of study because of the erosion of long-held views and dogmas in biology. Together TEI and epigenetics have contributed to the overwhelming amount of evidence for the Weismann barrier to be laid to rest, and have encouraged the revisitation and refinement of concepts such as the central dogma of molecular biology. Here, we will start by framing the discourse through the lens of Waddington's understanding of the relationship between genotype and phenotype and explore how progress in the field of TEI and research on lived experiences such as stress and environmental exposure have brought renewed attention to the concept of soft inheritance.

II. Waddington and the Definition of the Epigenome

In his seminal 1942 publication, "The Epigenotype", Conrad H. Waddington described the study of mechanisms that exist between genotypes and the phenotypic effects they bring about. Specifically, Waddington provided a prototype for a definition of epigenetics by stating that it refers to "the causal mechanisms at work […] linked together in a network […] by which the genes of the genotype bring about phenotypic effects." (Waddington, 1942). Thus, Waddington theorized, in a way akin to modern systems biology, that the developmental processes existing in this space form a network such that early perturbations could funnel to downstream consequences on phenotype. Waddington mentions the example of the 'grey-lethal' that prohibits the absorption of bone which has repercussions on other body systems (Grunberg, 1938). For the teeth in particular, impaired coordination and delayed calcification prevents the proper mastication of food. The lack of bone absorption also creates added pressure on nerves in the lower jaw and prevents the animal from taking

liquids, leading to starvation and death. Thus, the spontaneous ‘grey-lethal’ mutation of the gene disrupts bone absorption which in turn leads to neuralgic pain and death. From our current perspective, this example has very little to do with our present use of the term epigenetics.

Waddington’s concept of the epigenotype was deeply influenced by the current of thoughts in embryology and the debates around the nature and position of the components responsible for carrying out an organism’s developmental plan (Felsenfeld, 2014). Obviously, since Waddington’s original framework, and with the molecularization of biology, the definition of epigenetics has shifted from its focus on genotype-phenotype interactions towards the stability of expression states and cellular inheritance. It was verified that DNA methylation sites were palindromic, and that DNA methyltransferases were responsible for methylation of unmodified or hemi-methylated DNA (reviewed in Goll & Bestor, 2005). Importantly, these DNA methylation marks are copied on daughter strands after replication, which results in the transmission of the methylated state to future cellular generations (Goll & Bestor, 2005). This finding has led to the insertion of heritability into the definition of epigenetics and, in 1996, Riggs reinterpreted epigenetics as “the study of mitotically or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence” which has become the near standard definition of epigenetics (Riggs and Porter, 1996). Thus, the shift in definition of epigenetics opened a space for TEI to grow as an area of investigation: if the epigenetic marks are heritable then what molecular mechanisms exist that allow them to be transmitted? If some epigenetic marks are stable over several or many generations, and considering that DNA mutations are reversible, then what truly separates DNA-based heredity from TEI?

III. Revisiting the Central Dogma of Molecular Biology

As the definition of epigenetics shifted, so did the central dogma of biology. First defined by Francis Crick in 1957, the central dogma explains the direction of flow for genetic information in our cells. In its purest form, it translates to “DNA makes RNA, and RNA makes protein.” (Crick, 1958; Crick, 1970). Crick also specified that “the transfer of information from nucleic acid to nucleic acid, or from nucleic acid to protein may be possible, but transfer from protein to protein, or from protein to nucleic acid is impossible.” However, epigenetic pathways conflict with this rigidity and have transformed our interpretation of the genome at large. By altering the patterns of DNA methylation and that of histone modifications and non-coding RNAs (ncRNAs), the epigenetic machinery of writers, erasers, and readers directs in what cellular context, and when, specific genes should be expressed (Gillette and Hill, 2015). Similarly, mRNAs are also subject to posttranslational modification to both modulate gene expression and control their metabolism (Frye et al., 2016). For example, established by a multiprotein writer complex, N6-methyladenosine (m6A) is the most abundant modification of eukaryotic mRNAs and directly and indirectly affects the binding of various reader proteins, which either target mRNAs for degradation or translation (Yue et al, 2015). Recent studies have focused on the role of m6A during development for embryonic and adult stem cell differentiation (Roundtree et al., 2017). Specifically, m6A marks transcripts that contain vital developmental regulators to ensure proper transcriptome switching during cell

fate transitions. Other work indicates that m6A could interact with chromatin regulatory complexes and long noncoding RNAs to influence transcription as well (Patil et al., 2018).

Finally, ncRNAs also play a central role in the epigenetic regulation of chromatin states. In the fission yeast *S. pombe*, small interfering RNA targets and silences the repetitive pericentromeric region (Reinhart and Bartel, 2002). To accomplish this, three interacting protein complexes are involved. The RITS complex first determines the genomic location of the heterochromatin (Li et al., 2009). Then, the RNA-directed RNA polymerase complex (RDRC) amplifies small RNAs from the selected locus (Motamedi et al., 2004). Finally, the Clr4-containing complex establishes the heterochromatic mark (Zhang et al, 2008). To maintain silencing of the heterochromatic locus, transcription is necessary: the pericentromeric transcripts initially recognized by the RITS complex are synthesized into dsRNA and processed into new siRNAs that load additional RITS complexes, creating a reinforcing loop (Colmenares et al., 2007). The RITS complex also recruits other writers to promote histone deacetylation and H3K9 methylation (Moazed, 2009). In another well-understood example, in female mammals, the long non-coding RNA Xist plays a vital role in X chromosome inactivation. Xist-mediated silencing requires the presence of Xist A-repeats, which are structurally conserved (Wutz et al., 2002). As Xist spreads, it directly recruits polycomb repressive complex 2 (PRC2) that mediates the tri-methylation of H3K27 (Engreitz et al., 2013).

Thus, while sequence-based information may follow the unidirectional nature of Crick's central dogma, epigenetic mechanisms significantly add complexity to, and transform, the absolute linear schematic of the central dogma to resemble a molecularized version of Waddington's network.

IV. The End of the Weismann Barrier

While other concepts and dogmas may have been refined by epigenetics and TEI over time, no others have been affected as much as the Weismann barrier (Bline et al, 2021). The Weismann Barrier refers to the unidirectional and irreversible flow of developmental potential from germline to soma and has informed discussion about evolutionary genetic inheritance for much of the past century. However, recent transgenerational epigenetic inheritance research has refuted core tenets of the theory and indicated a larger role for environmental influence than previously held. The concept of a barrier originates from Weissman's germ plasm theory, which he used to justify how organisms remain relatively constant through generations but adapt to their environment over evolutionary time (Weissmann, 1893). He argued that after fertilization, a zygote had two paths for replication. The first choice was "embryonic" cell division, where daughter cells received some parts of the nuclear content. The resultant "idioplasm" gave rise to bodily tissues of the organism. The second choice was "ordinary" cell division, where the daughter cell received all nuclear contents of the parent. Here, a "reserve" germ plasm was produced, to be further transmitted to new generations. Importantly, Weismann postulated that idioplasm could under no circumstances be reconstructed into germ plasm. Therefore, any bodily changes brought about by external stressors during an organism's lifespan would not be passed on to their children. This inability of idioplasm to revert to germ plasm and be inherited by

offspring necessitated the existence of a barrier that prevented interaction between the two, which was later named the Weismann Barrier.

While the Weismann Barrier hinges on the separation of germ cells and somatic cells, recent studies have demonstrated that the two interact and exchange epigenetic information creating an additional source of heredity shaped by the parental environment. Multiple groups have now demonstrated and characterized the transfer of small RNAs between somatic and germline cells in mammals (Bohacek and Mansuy, 2015). For instance, in mice, metabolic tracing successfully verified that caput epididymosomes transport small RNA cargos initially synthesized in the epididymal epithelium to spermatozoa (Sharma et al., 2018). The content of these cargos is altered based on the various stress conditions or dietary perturbations encountered by the father preconception. With regards to models of stress, specifically in the “MSUS” paradigm – maternal separation coupled with unpredictable maternal stress –, zygotes injected with sperm RNAs from males subjected to MSUS give rise to offspring exhibit depression-like symptoms, specifically an increased tendency to remain floating during a forced swim test, an established measure of passive coping (Sharma et al., 2014). Remarkably, in other studies, the same increase in floating time can be elicited transgenerationally (until the F3) when MSUS is applied during gestation (van Steenwyk et al., 2018). The ability for sperm to carry experiential information to the offspring is not limited to stress-related cues. Offspring generated from mice raised on high-fat diets show impaired glucose metabolism and a small 30–40 nt sperm RNA (tsRNAs) fractions was shown to be the primary mediator of such effects (Chen et al., 2016). Interestingly, the tsRNA cargo requires itself epigenetic modification as demonstrated by the dependence of the transmission of impaired glucose metabolism on active tRNA methyltransferase DNMT2 (Zhang et al., 2018), highlighting again the complex interplay and layering of epigenetic information.

In a recent elegant set of experiments, van Steenwyk and colleagues showed that early life trauma in mice and humans raises specific lipid metabolite species in the serum that have the ability to activate PPARγ in sperm. Interestingly, injection in male mice of serum from mice subjected to MSUS or of a PPARγ agonist is sufficient to recreate the MSUS-induced glycemic deregulation in offspring (van Steenwyk et al., 2020). Together, these tantalizing developments in the field of TEI go exactly against the concept of the Weismann barrier: external influences on the soma can be physically transferred to the germ cells and be inherited by the offspring.

V. The Inheritance of Acquired Characteristics and the Return of Soft Inheritance

While new advances in the field of TEI are putting some old concepts to rest, they are also concomitantly reviving others that had largely been abandoned. In interesting ways, TEI resembles the concepts underlying the theory of inheritance of acquired characteristics, a common belief among eighteenth and nineteenth-century naturalists until it was mostly discarded for Darwin’s views of evolution and the Mendel, Boveri-Sutton, Morgan principles of heredity. The theory of inheritance of acquired characteristics, or

the ability for acquired characteristics during an organism's lifetime to be passed to their offspring, has long been associated with Jean Baptiste-Lamarck, even though most of the underlying principles of the theory were not his own (Burkhardt, 2013). Instead, Lamarck simply delineated specific conditions necessary for it to occur. Unlike his contemporaries, he argued that organisms took on new forms because of environmentally-shaped habits they acquired and not vice versa. To support this, Lamarck described how the webbed feet of the wading bird resulted from its continual exposure to sinking in mire when searching for prey. The bird will get in the habit of contracting its legs to elongate itself, and after successive generations this habit will be biology encoded in the species. Conversely, he postulated that constant disuse of an organ or part would cause it to deteriorate until it finally disappears.

While these ideas were eventually dismissed in favor of Darwinian views of evolution, the growth of TEI has signaled the return of a modernized version of Lamarckism: soft inheritance. Soft inheritance, bolstered by a growing body of evidence that variation in epigenetic states is not random but rather initiated and guided by the environment, posits that environment cues can influence hereditary information. While it remains a challenge to comprehensively identify the mechanisms of epigenetic inheritance from other environmental cues, the aforementioned studies indicate that parental lived experience such as stress can impact the health of descendants spanning several generations.

Interestingly, for soft inheritance and TEI to align at the molecular level, yet another concept needed refining: the ability of the mammalian early zygotes and early germ cells, termed Primordial Germ Cells (PGCs), to profoundly reprogram their epigenome, thereby producing an epigenetic "blank slate" (Messerschmidt et al, 2014). However, this "blank slate" specifically refers to the waves of DNA demethylation during early development while other epigenetic marks do not see reprogramming to a similar extent. Furthermore, even DNA methylation is not completely lost, it is reduced to around 10%, instead being actively maintained at critical genomic regions, such as repetitive elements (Tang et al, 2016).

The ability for environmental information to cause detectable and heritable alterations to the epigenome has now been described in a multitude of model organisms and involve all three types of epigenetic modifications. For example, in nematodes, the plastic component Bisphenol A causes transgenerational reproductive defects that are dependent on two histone modifications, H3K9me3 and H3K27me3 (Camacho et al, 2018; Weinhouse et al, 2018). Endocrine disruptors also lead to detectable transgenerational changes in DNA methylation in Zebrafish (Akemann et al, 2020) as well as in rats (Gillette et al, 2018). In the latter study, the authors examined the number of Differentially Methylated Regions (DMRs) occurring in sperm and specific brain nuclei involved in stress response and social behavior caused by *in utero* exposure to two endocrine disruptors Vinclozolin and the polychlorinated biphenyl (PCB) mixture A1221. They observed a high number of DMRs in the sperm, and to a lesser extent also in the brain regions, of male F1 and F3 progeny (Gillette et al, 2018). Remarkably, there was substantial overlap in the number and direction (hyper vs hypo-methylation) of the DMRs in sperm between F1 and F3 generations. This work opens exciting avenues to investigate whether in mammals, DMRs are maintained "as is" across

generation or whether a relay-mechanism exist that would involve cross-talks with other epigenetic marks or other mechanisms.

VI. Conclusion

While the examples we have examined in this paper have been confined to stress, diet, and environmental chemicals, the field of TEI encompasses many other types of environmental information. However, the field still suffers from a relative fragmentation of the research that forms it: fragmentation by model organism, type of epigenetic modification, environmental cue, and sex. Questions of applicability of the model organisms to humans are also not to be ignored, and continued examination of human cohorts, such as the often-cited example of the Dutch Hunger Winter study, while difficult, will provide critical proof of the relevance of findings in other model systems. Nonetheless, advances in the fields of epigenetics and TEI have already reshaped, or put to rest, numerous views previously considered as rules and/or central to biology.

Acknowledgements

P.A. is supported by the John Templeton Foundation, NIEHS R01 ES027487, and the Burroughs Wellcome Fund.

References

Akemann C, Meyer DN, Gurdziel K, Baker TR(2020). TCDD-induced multi- and transgenerational changes in the methylome of male zebrafish gonads. Environ Epigenet. 2020 Sep 27;6(1):dvaa010. doi: 10.1093/eep/dvaa010. [PubMed: 33214906]

Bline AP, Le Goff A, Allard P (2020). What Is Lost in the Weismann Barrier?. J Dev Biol. 2020 Dec; 8(4): 35. Published online 2020 Dec 16. doi: 10.3390/jdb8040035

Bohacek J, & Mansuy IM (2015). Molecular insights into transgenerational non-genetic inheritance of acquired behaviours. Nature reviews. Genetics, 16(11), 641–652. 10.1038/nrg3964

Burkhardt RW Jr (2013). Lamarck, evolution, and the inheritance of acquired characters. Genetics, 194(4), 793–805. 10.1534/genetics.113.151852 [PubMed: 23908372]

Camacho J, Truong L, Kurt Z, Chen YW, Morselli M, Gutierrez G, Pellegrini M, Yang X, & Allard P (2018). The Memory of Environmental Chemical Exposure in C. elegans Is Dependent on the Jumonji Demethylases jmjd-2 and jmjd-3/utx-1. Cell reports, 23(8), 2392–2404. 10.1016/j.celrep.2018.04.078 [PubMed: 29791850]

Chen Q, Yan M, Cao Z, Li X, Zhang Y, Shi J, Feng GH, Peng H, Zhang X, Zhang Y, Qian J, Duan E, Zhai Q, & Zhou Q (2016). Sperm tsRNAs contribute to intergenerational inheritance of an acquired metabolic disorder. Science (New York, N.Y.), 351(6271), 397–400. 10.1126/science.aad7977

Colmenares SU, Buker SM, Buhler M, Dlakić M, & Moazed D (2007). Coupling of double-stranded RNA synthesis and siRNA generation in fission yeast RNAi. Molecular cell, 27(3), 449–461. 10.1016/j.molcel.2007.07.007 [PubMed: 17658285]

Crick FH (1958, 1). On protein synthesis. In Symp Soc Exp Biol (Vol. 12, No. 138–63, p. 8).

Crick FH (1970). Central Dogma of Molecular Biology. Nature, 227(5258), 561–563. 10.1038/227561a0 [PubMed: 4913914]

Engreitz JM, Pandya-Jones A, McDonel P, Shishkin A, Sirokman K, Surka C, Kadri S, Xing J, Goren A, Lander ES, Plath K, & Guttman M (2013). The Xist lncRNA exploits three-dimensional genome architecture to spread across the X chromosome. Science (New York, N.Y.), 341(6147), 1237973. 10.1126/science.1237973

Felsenfeld G (2014). A brief history of epigenetics. Cold Spring Harbor perspectives in biology, 6(1), a018200. 10.1101/cshperspect.a018200 [PubMed: 24384572]

Frye M, Harada BT, Behm M, & He C (2018). RNA modifications modulate gene expression during development. Science, 361(6409), 1346–1349. 10.1126/science.aau1646 [PubMed: 30262497]

Gapp K, van Steenwyk G, Germain PL et al. Alterations in sperm long RNA contribute to the epigenetic inheritance of the effects of postnatal trauma. Mol Psychiatry 25, 2162–2174 (2020). 10.1038/s41380-018-0271-6 [PubMed: 30374190]

Gillette R, Son MJ, Ton L, Gore AC, Crews D (2018) Passing experiences on to future generations: endocrine disruptors and transgenerational inheritance of epimutations in brain and sperm. Epigenetics. 2018;13(10–11):1106–1126. doi: 10.1080/15592294.2018.1543506. [PubMed: 30444163]

Gillette TG, & Hill JA (2015). Readers, writers, and erasers: chromatin as the whiteboard of heart disease. Circulation research, 116(7), 1245–1253. 10.1161/CIRCRESAHA.116.303630 [PubMed: 25814685]

Goll MG, Bestor TH (2005). Eukaryotic cytosine methyltransferases. Annu Rev Biochem. 2005;74:481–514. doi: 10.1146/annurev.biochem.74.010904.153721. [PubMed: 15952895]

Jawaid A, Roszkowski M, & Mansuy IM (2018). Transgenerational Epigenetics of Traumatic Stress. Progress in molecular biology and translational science, 158, 273–298. 10.1016/bs.pmbts.2018.03.003 [PubMed: 30072057]

Li H, Motamedi MR, Yip CK, Wang Z, Walz T, Patel DJ, & Moazed D (2009). An alpha motif at Tas3 C terminus mediates RITS cis spreading and promotes heterochromatic gene silencing. Molecular cell, 34(2), 155–167. 10.1016/j.molcel.2009.02.032 [PubMed: 19394293]

Messerschmidt DM, Knowles DB, Solter D (2014). DNA methylation dynamics during epigenetic reprogramming in the germline and preimplantation embryos. Genes Dev. 2014 Apr 15;28(8):812–28. doi: 10.1101/gad.234294.113. [PubMed: 24736841]

Moazed D (2009). Small RNAs in transcriptional gene silencing and genome defence. Nature, 457(7228), 413–420. 10.1038/nature07756 [PubMed: 19158787]

Motamedi MR, Verdel A, Colmenares SU, Gerber SA, Gygi SP, & Moazed D (2004). Two RNAi complexes, RITS and RDRC, physically interact and localize to noncoding centromeric RNAs. Cell, 119(6), 789–802. 10.1016/j.cell.2004.11.034 [PubMed: 15607976]

Patil DP, Chen CK, Pickering BF, Chow A, Jackson C, Guttman M, & Jaffrey SR (2016). m(6)A RNA methylation promotes XIST-mediated transcriptional repression. Nature, 537(7620), 369–373. 10.1038/nature19342 [PubMed: 27602518]

Reinhart BJ, & Bartel DP (2002). Small RNAs correspond to centromere heterochromatic repeats. Science.

Riggs AD, & Porter TN (1996). Overview of epigenetic mechanisms. Cold Spring Harbor monograph series, 32, 29–46.

Roundtree IA, Evans ME, Pan T, & He C (2017). Dynamic RNA Modifications in Gene Expression Regulation. Cell, 169(7), 1187–1200. 10.1016/j.cell.2017.05.045 [PubMed: 28622506]

Sharma U, & Rando OJ (2014). Father-son chats: inheriting stress through sperm RNA. Cell metabolism, 19(6), 894–895. 10.1016/j.cmet.2014.05.015 [PubMed: 24896534]

Sharma U, Sun F, Conine CC, Reichholf B, Kukreja S, Herzog VA, Ameres SL, & Rando OJ (2018). Small RNAs Are Trafficked from the Epididymis to Developing Mammalian Sperm. Developmental cell, 46(4), 481–494.e6. 10.1016/j.devcel.2018.06.023 [PubMed: 30057273]

Stein Z, Susser M, Saenger G, & Marolla F (1975). Famine and human development: The Dutch hunger winter of 1944–1945. Oxford University Press.

Tang WWC, Kobayashi T, Irie N, Dietmann S, Surani MA (2016). Specification and epigenetic programming of the human germ line. Nat Rev Genet.. 2016 Oct;17(10): 585–600. doi: 10.1038/nrg.2016.88. [PubMed: 27573372]

van Steenwyk G, Roszkowski M, Manuella F, Franklin TB, & Mansuy IM (2018). Transgenerational inheritance of behavioral and metabolic effects of paternal exposure to traumatic stress in early postnatal life: evidence in the 4th generation. Environmental epigenetics, 4(2), dvy023. 10.1093/eep/dvy023 [PubMed: 30349741]

van Steenwyk G, Gapp K, Jawaid A, Germain PL, Manuella F, Tanwar DK, Zamboni N, Gaur N, Efimova A, Thumfart KM, Miska EA, & Mansuy IM (2020). Involvement of circulating factors

in the transmission of paternal experiences through the germline. The EMBO journal, 39(23), e104579. 10.15252/embj.2020104579 [PubMed: 33034389]

Waddington CH (2012). The epigenotype. 1942. International Journal of Epidemiology, 41(1), 10–13. 10.1093/ije/dyr184 [PubMed: 22186258]

Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, & Meaney MJ (2004). Epigenetic programming by maternal behavior. Nature neuroscience, 7(8), 847–854. 10.1038/nn1276 [PubMed: 15220929]

Weinhouse C, Truong L, Meyer JN, Allard P Caenorhabditis elegans as an emerging model system in environmental epigenetics. Environmental and molecular mutagenesis 59 (7), 560–575. [PubMed: 30091255]

Weismann A (1893). The Germplasm: A Theory of Heredity. Charles Scribner's Sons; New York, NY, USA: 1893

Wutz A, Rasmussen TP, & Jaenisch R (2002). Chromosomal silencing and localization are mediated by different domains of Xist RNA. Nature genetics, 30(2), 167–174. 10.1038/ng820 [PubMed: 11780141]

Yue Y, Liu J, He C (2015). RNA N6-methyladenosine methylation in post-transcriptional gene expression regulation. Genes Dev. 2015 Jul 1; 29(13): 1343–1355. doi: 10.1101/gad.262766.115 [PubMed: 26159994]

Zhang K, Mosch K, Fischle W, Grewal SIS (2008). Roles of the Clr4 methyltransferase complex in nucleation, spreading and maintenance of heterochromatin. Nat Struct Mol Biol. 2008 Apr;15(4):381–8. doi: 10.1038/nsmb.1406. [PubMed: 18345014]

Zhang Y, Zhang X, Shi J, Tuorto F, Li X, Liu Y, Liebers R, Zhang L, Qu Y, Qian J, Pahima M, Liu Y, Yan M, Cao Z, Lei X, Cao Y, Peng H, Liu S, Wang Y, Zheng H, … Chen Q (2018). Dnmt2 mediates intergenerational transmission of paternally acquired metabolic disorders through sperm small non-coding RNAs. Nature cell biology, 20(5), 535–540. 10.1038/s41556-018-0087-2 [PubMed: 29695786]