

Exploring the Interconnected Mechanisms of Transgenerational Epigenetic Inheritance

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ABSTRACT

It is estimated that around 70% of all adults around the world have faced trauma in their lives (Benjet et al., 2016). Trauma can cause individuals to undergo epigenetic changes which can lead to health complications in the future (Alegría-Torres et al., 2011). Epigenetics is defined as the study of molecular modifications to DNA through DNA methylation, histone modifications, and non-coding RNAs that can regulate gene expression independent of DNA sequences (Li, 2021). New evidence suggests that epigenetic changes may be passed down to offspring. However, the exact pathway for transgenerational epigenetic inheritance to occur is unknown. While existing theories, including intrauterine programming, miRNA-mediated pathways, and genomic imprinting, offer possible pathways, none can fully account for the spectrum of transgenerational inheritance. This paper will review the three models proposed and will explore the possibility of their combined influence on transgenerational epigenetic inheritance. Exploring epigenetic mechanisms can help offer potential intervention points to relieve the negative impact of trauma on several generations.

Introduction

Epigenetics is the study of heritable changes in gene function that do not involve alterations to DNA sequences through DNA methylation, histone modifications, and non-coding RNAs (Weinhold, 2006). DNA methylation occurs when a methyl group (CH₃) is added to a DNA molecule which then either activates or inhibits gene expression (Agrawal et al., 2007). Histone modifications are the addition or removal of chemical groups, such as acetyl, methyl, or phosphate groups, to specific amino acids in the histone proteins (Bannister & Kouzarides, 2011). These modifications can influence the structure of chromatin and as a result, gene expression (Bannister & Kouzarides, 2011). Non-coding RNA are molecules not directly involved in protein-coding and can guide histone-modifying enzymes to specific genomic regions, influencing the addition or removal of chemical groups on histone proteins (Bure et al., 2022). They can also interact with proteins involved in DNA methylation, influencing DNA methylation patterns (Bure et al., 2022).

On average an individual faces around 3 traumatic events in their lifetime (Kessler et al., 2017). Existing research shows that parental environmental experiences or trauma can alter their epigenome. For example, a study has reported a relationship between early life stress and changes in the DNA methylation of many genes such as the glucocorticoid receptor gene and the serotonin 1A receptor (Toraño et al., 2016). These trauma-induced changes have also been found to be passed down to offspring (Youssef et al., 2018). In a study looking at Lebanon war combat stress reaction casualties, scientists found that individuals who were offspring of Holocaust survivors had a higher rate of developing post-traumatic stress disorder (PTSD) compared to those who witnessed the Lebanon war but did not have parents who were exposed to the Holocaust (Solomon et al., 1988). Another example of trauma-induced inheritance is seen in a study looking at the Överkalix cohort case (Kaati et al., 2002). They found that the grandparents' access to food affected the progeny's susceptibility to disease and mortality (Kaati et al., 2002). Despite the progeny's changes, such as increased diabetes mortality (Kaati et al., 2002), human studies have not ruled out ecological and cultural factors that may influence generational changes. However, inherited epigenetic changes are closer to being established in animal models. For

example, in a rat model that conditioned rats to fear a cherry blossom scent, scientists found that both F1 and F2 generations experienced epigenetic changes such as an increase in the number of M71-expressing olfactory sensory neurons which increased their behavioral sensitivity to this scent (Dias & Ressler, 2014). Inherited epigenetics can have severe implications, hinting at the fact that trauma can not only affect one individual but also the generations that come after them. Yet, it is not clear how these epigenetic changes are passed down. There are numerous transgenerational theories proposed but the most supported theories include the direct inheritance of DNA methylation through intrauterine programming (Deodati et al., 2019; Jiang et al., 2020), inheritance via altered sperm miRNA and non-coding RNA (Lee & Conine, 2022; Raad et al., 2021), as well as genomic imprinting (Grandjean et al., 2009; MacDonald, 2012). However, these theories independently cannot explain how trauma-induced epigenetic changes experienced by either the father or the mother can be passed down. Therefore, this review highlights potential mechanisms in which transgenerational inheritance may occur.

Intrauterine Programming

One promising theory to explain transgenerational inheritance is through intrauterine programming which is when the mother faces trauma that can affect the uterine environment ultimately influencing fetal development (Sedaghat et al., 2015). During mammalian development, the intrauterine environment can significantly affect fetal development (Gluckman et al., 2008). For example, fetal growth size is generally matched to the mother's body size rather than through genetic disposition (Gluckman et al., 2008). Additionally, it has been found that past trauma before conception can influence birth weight (Blackmore et al., 2016). The mother can also pass down environmental information such as nutrition availability, the fetus can take cues from its mother about her health and physical state (Gluckman et al., 2008). This could potentially serve as a way to prepare the offspring for its future environment. Therefore, these cues may serve as a possible mechanism for epigenetic information to pass to the fetus. Environmental cues include changes in the mother's hypothalamic-pituitary-adrenal (HPA) axis which is the stress response system that regulates the release of glucocorticoids which can redirect energy resources to meet demand (Herman et al., 2016). Recent studies suggest that trauma before pregnancy may lead to permanent modifications of the mother's HPA axis (Cordero et al., 2017; Wahbeh and Oken, 2013). In a study looking at Holocaust survivors, they found that parental post-traumatic stress disorder (PTSD) is associated with alterations in HPA axis function in offspring, including enhanced cortisol suppression and lower baseline cortisol levels (Yehuda et al., 2014). Excessive maternal stress can lead to a change in levels of cortisol and placental corticotropin-releasing hormone (CRH) hormones which play a role in the development of the fetus' HPA axis (Howland et al., 2017). The CRH hormones are the primary regulator of the HPA axis which releases and controls cortisol production (Allen & Sharma, 2023). Cortisol mobilizes the body's physiological and psychological resources to react to the stressor and maintain homeostasis (Howland et al., 2017). Cortisol is also involved in a feedback loop that maintains the regularity of CRH and adrenocorticotropic hormone (ACTH) hormone production (Raff & Carroll, 2015). Excessive changes in cortisol levels can cause the dysregulation of the HPA axis and terminate the stress response (Howland et al., 2017), a direct example of how intrauterine programming may influence epigenetic changes. Additionally, another study looking at the Dutch Famine suggested that intrauterine programming influences epigenetic changes (Painter et al., 2008). Evidence suggests that the Dutch famine induced specific trauma-related inheritance, where the F1 and F2 generations of pregnant mothers exposed to famine exhibited increased susceptibility to chronic diseases (Painter et al., 2008). However, these findings do not show the same epigenetic alterations in the trauma-exposed and offspring generations (Painter et al., 2008). These changes are also less pronounced in the F2 generation (Painter et al., 2008). These effects may have come from malnutrition that mothers faced, causing a hostile uterine milieu that affected the growth of the fetus. Maternal malnutrition can lead to intrauterine growth restriction (IUGR) which can affect the transfer of nutrients and oxygen to the fetus, as well as the vascular growth

and functional capacity of the placenta (Sinha et al., 2018). This can lead to increased mortality, delayed motor development, and cognitive dysfunction in the offspring (Sinha et al., 2018). Yet, there are instances where famine has caused identifiable epigenetic changes (Jiang et al., 2020). For example, a study investigating the famine in Suihua, China found that there were 19 differentially methylated sites in both the F1 and F2 generations, neither of which were directly exposed to the famine (Jiang et al., 2020), suggesting that these alterations after prenatal famine exposure might be subject to intergenerational transmission. Seventeen of these sites were located in genes that played a critical role in kidney development, glomerular protection, and renal cell survival (Jiang et al., 2020). This demonstrates that environmental cues may alter epigenetics in the mother which are then passed down for multiple generations because it changes the mother's uterine environment causing the same epigenetic changes seen in the next generation. Regardless, this method does not account for the epigenetic changes seen in offspring where the father was exposed to trauma, showing that intrauterine programming cannot account for all epigenetic inheritance.

How Non-Coding RNA May Contribute to Heritable Epigenetics

Another theory for inherited epigenetic change is through non-coding RNA: microRNAs (miRNA) and transfer RNA fragments which can regulate gene expression (Ying et al., 2008). Though these fragments were originally disregarded as remnants of degradation, they are now recognized as a class of small regulatory RNAs with the ability to contribute non-genetically inherited information intergenerationally (Lee & Conine, 2022). For example, a rat model study exposed female rats (F0) to DDT during gestation and they were bred to produce F1, F2, and F3 generations (Skinner et al., 2018). Researchers found alterations in non-coding RNA expression in sperm samples; F1 and F3 generations had higher numbers of long non-coding RNA(ncRNA) than the F2 generation (Skinner et al., 2018). F1 and F3 generations had higher numbers of small ncRNA than the F2 generation (Skinner et al., 2018). Long ncRNA recruits chromatin-remodeling complexes, which mediate epigenetic changes (Kaikkonen et al., 2011). Small ncRNAs might trigger epigenetic gene expression changes (Duempelmann et al., 2020). The F3 generation was completely unexposed and yet still showed transgenerationally inherited altered non-coding RNA in sperm samples (Skinner et al., 2018). A recent rat model identified nine miRNA (miR-29c, miR-30a, miR-30c, miR-32, miR-193-5p, miR-204, miR-375, miR-5323p, and miR-698) that were increased in the sperm of stressed fathers (Rodgers et al., 2015). These miRNAs were associated with reduced stress axis reactivity in the offspring's HPA axis and produced a phenotype nearly identical to the paternal stress model (Rodgers et al., 2015). Another study involving rats has shown that a paternal diet can influence the number of small RNA in sperm, leading to metabolic disorders in offspring (Chen et al., 2016). This evidence suggests that RNA from the father may influence the development of the offspring. In addition, another study found that when miR-124, coding for the "giant phenotype", was zygotically injected in male mice mated with control females, the offspring were 30% larger than the controls (Grandjean et al., 2009). Additionally, when female mice were zygotically injected with miR-124 and mated with control mice, the offspring were similarly larger than controls (Grandjean et al., 2009). This evidence suggests that RNA-induced changes can occur through both male and female germlines. RNA inheritance may persist through multiple generations. In a rodent study, five generations of mice were fed a high-fat and high-sugar diet, which mimicked a Western diet (Raad et al., 2021). RNA from the first generation of mice demonstrated altered metabolic phenotypes, such as increased body weight, which was partially conserved in the F2 generation (Raad et al., 2021). Microinjections of RNA from the 5th-generation mice into naive zygotes demonstrated the conservation of the metabolic phenotypes produced by the Western diet in the 5th generation (Raad et al., 2021). This implies that the likelihood of inheritance increases if the stressor or trauma occurs over an extended period of time or multiple generations. Furthermore, additional studies suggest that miRNA alters gene expression in offspring (Rodgers et al., 2013). In another rodent study, researchers stressed mice for six weeks and recorded the increased expression of nine miRNAs (Rodgers et al., 2013). The progeny of the stressed mice had altered gene

expression and HPA axis sensitivity (Rodgers et al., 2013). The researchers then created synthetic miRNA that mimicked the miRNA from stressed mice and inserted it in naive zygotes (Rodgers et al., 2013). They found the same HPA sensitivity in these mice as the progeny of the stressed mice (Rodgers et al., 2013), suggesting that miRNA may underlie the mechanism of epigenetic inheritance. Human sperm miRNA may be similarly altered due to stress (Morgan et al., 2020). Some 1,579 similar RNA transcripts involved in spermatogenic functions were found in both humans and mice suggesting that rodent models could be suitable substitutes for human models (Bianchi et al., 2021). Inherited epigenetic changes are more clearly seen in a study where male mice were exposed to early life stress (Gapp et al., 2014). These mice had increased levels of several types of miRNA in their sperm, serum, hippocampus, and hypothalamus indicating that stress led to changes in miRNA (Gapp et al., 2014). The target of one of these altered miRNA (Catenin β 1) was downregulated in the F1 generation showing that stress from a previous generation may cause molecular changes in the offspring's brain (Gapp et al., 2014). However, the same epigenetic changes were not observed in the F0 and F1 generations (Gapp et al., 2014). Even if the F1 generation had the same altered miRNA it was not expressed in the F1 generation's sperm indicating that these changes may not be passed down for multiple generations.

Genomic Imprinting

An alternative theory for transgenerational epigenetic changes caused by trauma or stress is through genomic imprinting in germ cells that allows parents to pass down epigenetic changes via their imprinted loci (MacDonald, 2012). Trauma can influence different imprinted loci, for example, maternal depression can influence the methylation of Insulin-like Growth Factor 2 (IGF2) and its correlated gene (IGF2AS) (Vangeel et al., 2015). However, normally, genomic imprinting is essential for healthy prenatal growth and postnatal processes such as the regulation of the brain and behavior (Ferguson-Smith & Bourc'his, 2018). Genomic imprinting is defined as epigenetic modifications placed on genes that are heritable and influence how they are expressed based on the sex of the transmitting parent (Faisal et al., 2014). During a new life cycle, genomic imprints are established during the development of primordial germ cells (PGCs) based on the alleles from the mother and the father (Bajrami & Spiroski, 2016). They are maintained after fertilization as the zygote begins to divide with the help of protein complexes such as ZFP57 which is a zinc protein and TRIM28/ KAP1 which is an obligate co-factor that bind to imprinted control regions, which are specific clusters of genes, and preserve it during this division (Bajrami & Spiroski, 2016; Zuo et al., 2012). The imprints are then erased in the germ cells of the developing organism at an early stage, removing the epigenetic marks inherited by the previous generation (Seisenberger et al., 2013). They are re-established later in germ cell development through imprinted loci (Li & Sasaki, 2011). Lastly, they are "read", converting DNA methylation into differential gene expression (Ferguson-Smith & Bourc'his, 2018). As a result of this, there is a biased allelic expression, meaning that one allele (either maternal or paternal) is favored over the other in terms of gene expression (Ferguson-Smith & Bourc'his, 2018). This results in parent-specific epigenetic changes being passed down (Seisenberger et al., 2013). For example, the 15q11-q13 region of chromosome 15 is only imprinted/expressed paternally (Butler, 2011). If there is a deletion in this paternal region it can lead to Prader-Willi Syndrome (Driscoll et al., 2023). Since imprinted marks are transmitted through the germline to the next generation, if epigenetic marks are altered in response to a stressor, these changes can be passed on to future generations through the germline. One example of altered imprinted marks being inherited is seen in researcher Valérie Grandjean's rat model study where miRNA coding for the giant phenotype was injected into naive mice and increased the growth of the mice in the F1 and F2 generations (Grandjean et al., 2009). The maternally imprinted loci- IGF2 which codes for this insulin-like growth factor was passed down for two generations (Grandjean et al., 2009). Another example of the inheritance of imprinted marks can be seen in the results of a study done on the Dutch Famine (Tobi et al., 2009). The Insulin-like Growth Factor 2 (IGF2), Guanine Nucleotide binding protein, Alpha Stimulating activity polypeptide antisense RNA (GNAS-AS), and Maternally Expressed Gene 3 MEG3 (all imprinted loci) were hypermethylated in the

F1 generation (conceived during the famine-exposed prenatally) compared to their unexposed siblings (Tobi et al., 2009)

Discussion & Limitations

Despite the passing down of epigenetic changes, these modifications only lasted for a couple of generations before returning to the normal unexposed state (Gapp et al., 2014; Grandjean et al., 2009; Heard & Martienssen, 2014; Painter et al., 2008). In the Dutch Famine study, it was also found that the F1 generation exposed in the late gestation period only had one hypermethylated imprinted locus (Tobi et al., 2009). This suggests that the inherited epigenetic changes may only last until the environmental pressure (trauma) passes, and there may be a critical period during gestation that is most vulnerable to epigenetic modifications.

This critical period may occur during early gestation, previous studies define the periconceptual period as a critical window where exposures (trauma or stressors) can disrupt the normal physiological development of a cell, tissue, or organ of the fetus (Gluckman et al., 2008; Louis et al., 2008). This can also serve as a critical window for epigenetics because de-methylation of PGCs occurs by embryonic day 13.5 (Messerschmidt 2012). In males, the re-establishment of imprints occurs during spermatogenesis; in females, it begins during oogenesis (Kelsey & Feil, 2013). In another study that examined famine, DNA methylation, and sex-specific epigenetic changes, prenatal exposure to the famine resulted in a more pronounced impact on epigenetic changes where the prenatally-exposed individual had decreased methylation in the insulin-like growth factor 2 that regulates fetal and postnatal growth (INSIGF) region (Tobi et al., 2009). The changes in the methylation patterns at the INSIGF region provide support that the periconceptual period may be extremely susceptible to environmental influence, and this period may be a critical point for changes to occur in the epigenome.

Because all studies on transgenerational epigenetic inheritance show that epigenetic changes are eventually reversed we can conclude that they are dynamic; they are influenced by external factors and last until the environmental pressure dissipates. The dynamic nature of transgenerational epigenetic changes could provide an evolutionary advantage to prepare the next generation for the conditions they would face.

The sperm and egg may play a role in keeping track of these environmental conditions. Although the precise moment that epigenetic changes are re-established during oogenesis is not known, it is possible that when the F1 generation is developing in utero, the F1 germ cells are affected by the environmental pressure experienced by the F0 generation. Therefore, the F0 generational pressures may be passed down to the F2 generation by affecting the F1 generation's germ cells, particularly the process of oogenesis. MiRNA can also be affected by stress. A recent study demonstrated that there were increased levels of miR-15a in the blood of subjects exposed to childhood trauma compared to non-exposed individuals (Maffioletti et al., 2021).

Each model for transgenerational epigenetic inheritance has limitations, and each individual model cannot fully account for all instances of inheritance. Studies that supported intrauterine programming have shown that the same parental epigenetic changes are not passed down, and it cannot account for cases where the father experienced the trauma. Paternal changes can be either passed via the germline or through genomic imprinting. Non-coding RNA in sperm is the most commonly accepted path for paternal epigenetic changes to be passed down through the germline (Ghai & Kader, 2021). However, most evidence for transgenerational epigenetic inheritance via miRNA has been established through rat models, not human cases. Even though rat models can represent the epigenetic mechanisms in human cases, it does not fully capture the complexity of human genomics. For example, preliminary studies suggest that certain genes may be paternally expressed and regulated by maternal H3K27me3 in human embryos (Kobayashi, 2021), but these genes may not be imprinted in mice. The non-coding RNA in sperm method to pass down transgenerational epigenetic inheritance lacks strong human evidence. Genomic imprinting may account for both inherited maternal and paternal epigenetic changes, however, it is parent-dependent and only passes down changes in imprinted loci. By recognizing the

individual limitations of each model, it is possible that transgenerational epigenetic inheritance may involve a combination of intrauterine programming, miRNA, and genomic imprinting.

In fact, the Dutch Famine study suggests that multiple models may play a role in epigenetic changes caused by environmental pressures. It showed that the F1 generation exposed in the late gestation period had one imprinted hypermethylated locus, suggesting that this could have occurred through intrauterine programming because demethylation would have already occurred by late gestation. Intrauterine programming, therefore, can impact imprinted loci. It can also have an impact on miRNA expression. The uterine environment has various factors, including oxygen levels, nutrient availability, hormonal signals, and other conditions that can influence the expression of miRNAs in the developing fetus (Ali et al., 2021). For example, gestational hypertension has been associated with several changes in the fetus' miRNA expression including highly expressed cardiac miRNAs; miR-1, and miR-133a (Lock et al., 2017). From this, it can be concluded that all three mechanisms, intrauterine programming, miRNA, and genomic imprinting may influence each other and may account for the gaps in their mechanisms. Ultimately, we suggest they may all play a role in transgenerational epigenetic inheritance.

Conclusion

In conclusion, epigenetic inheritance may be an evolutionary advantage to prepare the next generation. The temporary nature of inherited epigenetic changes, observed across various studies, suggests a dynamic and adaptive system that responds to environmental pressures. The limitations in the reviewed models strongly suggest the interplay of intrauterine programming, miRNA pathways, and genomic imprinting. Together, these models contribute to transgenerational epigenetic changes. It is important to explore the complex interplay of the methods of transgenerational epigenetic inheritance because it can provide a deeper understanding of how trauma can affect multiple generations and a possible point at which intervention can mitigate the negative impact of trauma.

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