How Trauma Can Affect Future Generations Through Epigenetics

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Background

The DNA sequence is the fundamental unit of heritable information, however, its functional expression relies on regulatory signals that indicate how the sequence should be transcribed. These signals are known as epigenetic mechanisms, and they can act upon identical DNA sequences to generate different phenotypic outcomes (Fitz-James & Cavalli, 2022). Since these are heritable molecular signatures, it is important to denote the difference between intergenerational and transgenerational inheritance. Fitz-James & Cavalli (2022) describe intergenerational inheritance as when the parent organism within which an epigenetic change has occurred transmits this signal to its offspring, but it is not maintained. The signal is only present in the immediate offspring after direct exposure to the stimulus that incurred the change. In contrast, transgenerational transmission indicates the epigenetic markers have been maintained through generations—the F2 offspring in males or the F3 offspring in females because of exposure to the embryonic germline during development— even in the absence of the environmental cue (Fitz-James & Cavalli, 2022).

These cues can be caused by trauma or adverse experiences as we will discuss in this paper. We will also discuss various correlational studies that have been conducted to describe epigenetic inheritance in human populations due to adverse experiences: there is still a lack of human and mammalian model studies on the direct mechanisms of transgenerational epigenetic inheritance (Fitz-James & Cavalli, 2022). However, we must first understand some underlying mechanisms on the development and transmission of epigenetic signals.

Epigenetic Mechanisms and Their Modes of Inheritance (Fitz-James & Cavalli Review)

The first and most often discussed epigenetic mechanism is DNA methylation. In vertebrates, this primarily occurs through the methylation of cytosine phosphate guanine (CpG) dinucleotides. A de novo methyltransferase catalyzes the addition of a methyl group to the cytosine at the 5' position of the pyrimidine ring. This hemi-methylated DNA is recognized by a DNA maintenance methyltransferase resulting in methylation of the cytosine on the opposite strand. Methylation is maintained through cellular divisions and promotes the recruitment of histone modifiers such as histone deacetylases and chromatin remodelers like Mi-2 or BRM of the switch/sucrose non-fermenting family which often tend to repress transcription by binding and blocking promoter regions (Fitz-James & Cavalli, 2022).

The characteristics of histone modifications make them ideal candidates for epigenetic inheritance. They have the potential for self-propagation and the spreading of epigenetic signals to offspring through 'writer' and 'reader' functions. In broad terms, a 'writer' protein complex chemically modifies a target amino acid, namely lysine, on the amino acid tail of the histone. This can influence chromatin compaction either directly or by recruiting additional protein 'reader' complexes like histone methyltransferases or heterochromatin protein 1, permitting a cascade leading to transcriptional silencing (Fitz-James & Cavalli, 2022). There are many examples of histone modifications being inherited transgenerationally in the literature. For example, the H3 lysine 9 trimethylation modification is strongly associated with DNA methylation in vertebrates (Rose & Klose, 2014). However, there are further examples that show the inheritance of H3K9me epimutations due to caffeine exposure in the fungi *Schizosaccharomyces pombe* (Torres-Garcia et al., 2020). Finally, an intriguing study by Ciabrelli et al. (2017) found that the H3 lysine trimethylation differences in a transgene of fruit

flies could regulate the expression of a gene for eye colour. These histone modifications were transmitted and remembered across generations (Ciabrelli et al., 2017).

Non-coding RNAs (ncRNAs) are the third general epigenetic mechanism that may be transmitted across generations. NcRNAs generally act as secondary carriers of epigenetic information because their transcription is altered depending on chromatin modifications like DNA methylation or through histone modifications in the parent. Small RNAs (sRNAs) such as small-interfering RNA, with the assistance of Argonaute proteins, can recruit chromatin-modifying complexes to transcriptionally silence or activate various genes. In the sperm of animals, micro-RNAs (miRNAs) are commonly found in the cell after spermatogenesis and have drastic implications in the transmission of epigenetic signals through the degradation of specific mRNA transcripts during embryonic development (Fitz-James & Cavalli, 2022). This will be discussed later.

Lastly, it is important to recognize that Fitz-James & Cavalli (2022) characterize two mechanisms by which these epigenetic signals may be transmitted. The first is through replicative transmission, where the DNA is faithfully replicated with all of its epigenetic markers, such as DNA methylation and histone modifications, during meiosis as is seen in mitosis. However, this is not as likely in complex eukaryotes because these organisms experience genome-wide reprogramming during development, meaning many of these epigenetic mutations may initially be lost. Accordingly, in the second model epigenetic transmission is maintained through reconstructive transmission. Secondary signals such as the ncRNAs described above, or transcription factor binding, and the ‘memory’ of the spatial configuration of DNA within the nucleus through locus interactions all act to restore these epigenetic markers and thus exert their effects on the offspring (Fitz-James & Cavalli, 2022). Next, it is important to observe primary

studies that indicate possible mechanisms for how trauma can affect future generations by epigenetic inheritance both through maternal and paternal pathways.

Initial Epigenetic Trauma Mechanisms: DNA Methylation Revisited

There are a variety of different outcomes resulting from the alterations of DNA methylation. This can include hyper/hypomethylation of sites which normally experience some degree of methylation, as well as methylation at sites which were previously unmethylated. The mechanisms behind how stress hormones cause DNA methylation are not fully understood, but it has been shown that chronic exposure to stress hormones, such as cortisol, during childhood can lead to methylation of specific sites in the genome, epigenetically modifying DNA expression (Houtepen et al. 2016).

Some of the most well-documented epigenetic changes due to trauma is on the *NR3C1* gene coding for the glucocorticoid receptor (GR) protein which is responsible for binding with cortisol and other stress hormones/glucocorticoids. It has been noted that insufficient quantities of these glucocorticoid receptor proteins are connected to dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis. Additionally, many of the genes that have been noted to be potentially affected by early life trauma are in some way connected to the GR protein gene. For example, Matosin et al. (2018) found that a risk allele associated with the *FKBP5* gene can be affected by childhood trauma, which in turn up-regulates transcription of the gene. *FKBP5* is a gene which codes for heat shock protein 90 co-chaperone which plays a role in inhibiting GR function (Klengel et al. 2012). The gene itself has 16 splice variants with 8 coding exons and 7 alternate non-coding first exons which play a role in transcriptional regulation of the gene. It is these alternate first exons that experience differential methylation at many of their cytosine

phosphate guanine (CpG) sites, post early-life stress/trauma. These modifications often result in decreased GR protein expression which is accredited with impaired control of the HPA axis (Rizavi et al. 2023). Impaired control of the HPA axis can have detrimental effects on one's mental health, as it is responsible for stress and adrenal hormone regulation.

A study by Rizavi et al. (2023) investigated the relationship between glucocorticoid receptor (GR) gene expression, epigenetic modifications, and hypothalamic-pituitary-adrenal (HPA) axis dysfunction in teens who completed suicide. Researchers analyzed postmortem prefrontal cortex and hippocampus tissues, measuring mRNA levels and DNA enrichment of 5mC and 5hmC (5-methylcytosine and 5-hydroxymethyl cytosine respectively) in the GR-related genes *NR3C1* and *FKBP5*. Results revealed decreased GR mRNA from certain first exon variants in the prefrontal cortex of suicide-completers but not in the hippocampus. Additionally, suicide-completers had higher *FKBP5* mRNA with reduced levels of 5mC and increased levels of 5hmC near the transcriptional start site of the *FKBP5* gene, which may increase *FKBP5* expression and reduce *NR3C1* expression, ultimately reducing the concentration of GR proteins.

Maternal Trauma and Epigenetic Transmission

Pilkay et al. (2024) Study and Findings

Pilkay et al. (2024) Investigated whether newborn DNA methylation at specific sites, which has been previously associated with maternal childhood physical abuse by her father, affected the child's mental health and physical growth, as well as whether it mediated or moderated developmental outcomes. This study builds upon a previous study in which they had findings of epigenome-wide associations between newborn DNA methylation and maternal

childhood physical abuse according to her relationship with her abuser. They found different biological pathways were affected depending on whether the abuser was their father or mother.

This study specifically focuses on mothers who were abused by their fathers as children to examine the developmental outcomes of these specific pathways on their offspring. To determine the mothers' childhood abuse and demographic, a self-reported questionnaire was completed by each participant with one of the questions asking which parent was their abuser. Cord blood at the birth of each child was measured for DNA methylation using the HumanMethylation 450 BeadChip. They included the 60 targeted probes—identified in their previous study—within their analyses. Seven outcome variables were tested for child mental health and physical growth. Mental health was measured by indicators of anxiety and depression based on parent and school reports. Different separation anxiety symptoms were included to be an indicator of greater complexity of separation anxiety experienced by the child. The schools also reported on the degree to which the child was experiencing worries or fears. Child depression was based on the degree to which schools reported the child to be unhappy or tearful. Child physical growth was measured with adiposity rebound calculated by visual inspection of an upward trend in BMI (Pilkay et al., 2024).

The findings of their study indicated that increased DNA methylation at specific CpG sites in the ABAT and GRLX genes measured in newborn cord blood, which was previously associated with maternal physical abuse in childhood from her father, is also associated with increased separation anxiety symptoms scores in her child at the age of 7 regardless of sex. The gene LMNB1 saw reduced DNA methylation at its transcriptional start site. Due to its close connection with the ABAT gene, they suspected that the downregulation of the ABAT gene may have caused the upregulation of the LMNB gene. Unlike with separation anxiety, however, they

found statistically significant results in child fear and unhappiness in relation to difference of sex. Methylation at the HSPA2 gene in girls was negatively associated with the child having many fears, and methylation at the DAXX gene in boys had a positive association with the child having many fears. In their results/discussion, it is rarely mentioned, but from a few figure descriptions it appears as if adiposity rebound had no correlation to DNA methylation and in turn maternal childhood trauma (Pilkay et al., 2024). Overall their study suggests that maternal childhood trauma can be seen intergenerationally through DNA methylation at specific sites in their children, which can have lasting psychological effects.

However, there are some limitations to this study. The sample cohort was generally all of the same cultural background. It also may be hard to get truly accurate results when working with children and psychology reports being used are from the child's school. The method of rating different symptoms by schools on a scale from 0-2 (0-not true, 1-somewhat true, 2-certainly true) likely resulted in some inaccurate scaling for the extent of the child's symptoms. Though their relatively large sample size may have diminished the effect of potential errors.

Broeks et al. (2023) Study and Findings

Examined if there was a relationship between mothers who had experienced childhood trauma, current depressive or anxiety symptomatology, and recent life events with maternal and infant long-term cortisol levels three months postpartum. Alterations in stress regulation and function of the HPA axis during infancy could potentially be a predictor for psychopathology later in life. So the goal was to determine if maternal childhood trauma caused epigenetic alterations passed to their children that may negatively affect these children's abilities to regulate and control stress hormones at their hypothalamic-pituitary-adrenal axis.

Their data was collected from 89 mothers, all of which met the criteria for a lifetime depressive or anxiety disorder as well as childhood trauma. 49 infants were examined along with the mothers. Hair cortisol concentrations were quantified via liquid chromatography as well as tandem mass spectrometry three months postpartum. Hair was collected by cutting a small strand of hair as close as possible to the scalp to get the most recently produced hair that would depict cortisol levels for the desired time period. At an average growth rate of around 1 cm per month in adults, the bottom 3 cm of the hair strand was the target area. For infants, the proximal 3 cm of hair was used unless there was less than 3 cm available in which case the length was decreased. To determine if the mothers met the requirements for the studies they completed multiple questionnaires: Childhood Trauma Questionnaire, Edinburgh Postnatal Depression Scale, State-Trait Anxiety Inventory, and an Everyday Problem Checklist. They also included a large list of confounders when analyzing their data ranging from age to ethnicity to medication in the mothers, and a list of others in the infants.

From their results, they found no significant relationship between hair cortisol concentrations and maternal depressive and anxiety symptoms throughout pregnancy and at the time of cortisol sampling after birth. The same was found for any recent life events that may have affected cortisol levels. However, there was a positive curvilinear relationship between hair cortisol concentration and childhood trauma in the mothers.

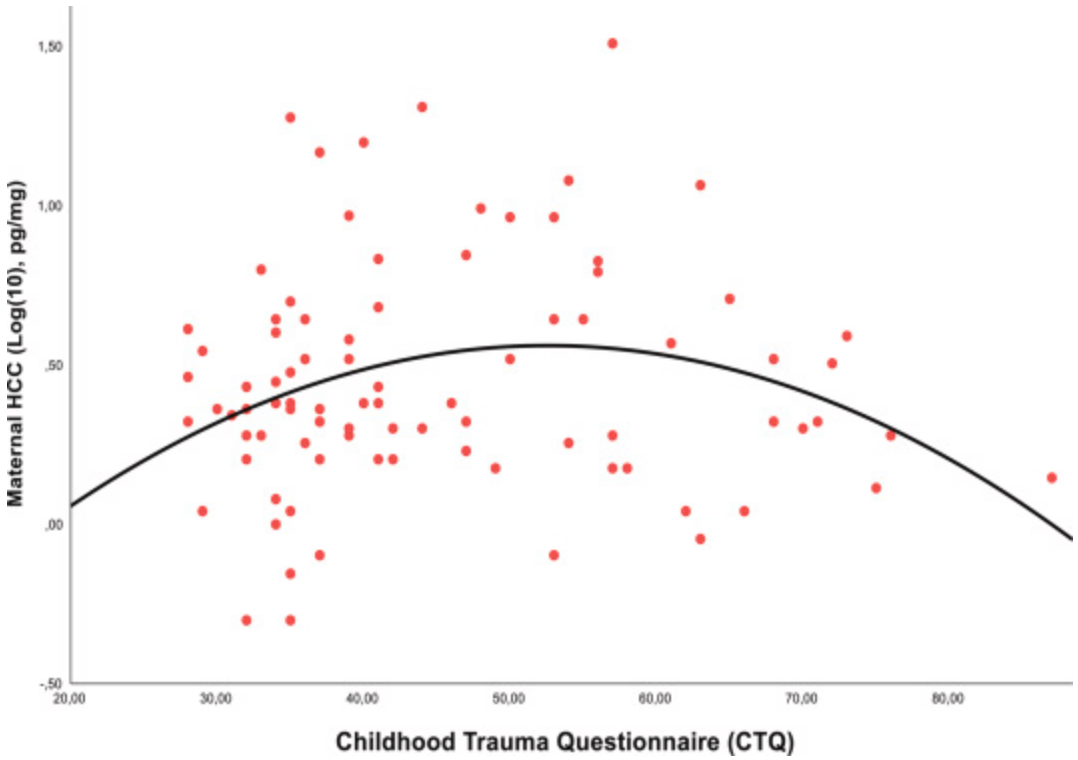

Figure 1. Scatterplot of the maternal hair cortisol concentrations (HCC) and the total score on the Childhood Trauma Questionnaire (CTQ) in mothers (N=83). Average CTQ scores on community samples are 38.78 (SD 14.98) and 45.91 (SD 18.79) in patient samples. (Broek et al. 2023).

Figure 1. shows this curvilinear relationship showing that mothers who had experienced the "high end" of trauma had similar cortisol concentrations to those who experienced little to no childhood trauma. While mothers who were subjected to mild-moderate childhood trauma show relatively higher cortisol concentrations. The reason that the most traumatized women are showing lower cortisol levels could be due to the fact that chronic stress by traumatization over time leads to glucocorticoid receptor desensitization, which results in hypocortisolism at the cellular level as seen in animal studies. However, what is interesting is that their study found a negative linear relationship between maternal childhood trauma and infant hair cortisol concentrations. While maternal mental health during pregnancy did not have a statistically significant effect on hair cortisol concentration in infants. This negative association between

childhood trauma in mothers and HCC in infants but not in any of the other examined maternal adversities suggests that the transgenerational effect of trauma influences the developing infants HPA axis more prominently than previously thought.

There were several limitations to this study, however. Many of the mothers were on antidepressant medication which Broek et al. could not properly control for. They also didn't control for any personality disorders. Furthermore, their method of identifying childhood trauma was based on a retrospective self-report measure, therefore not accounting for any recent or current stressors or trauma that may have impacted results.

Paternal Trauma Epigenetic Transmission Through Sperm RNA

The function and mechanism of germline epigenetic inheritance are especially enigmatic between father and offspring. Recently, sperm RNA, which was previously ignored, has been characterized as an additional source of parental hereditary information during fertilization of the oocyte (Wang et al., 2021). Despite a multitude of pioneering studies that show sperm RNA's influences on embryonic development, there is a lack of understanding of the direct mechanisms that might underlie the acquisition of a paternal phenotype. Wang et al. (2021) and Gapp et al. (2018) conducted studies that investigated this phenomenon, each examining the mechanisms through which paternal stress-induced phenotypes are epigenetically inherited in mice.

Wang et al. (2021) Study and Findings

Wang et al. (2021) explored the epigenetic inheritance of depressive-like behaviours, particularly focusing on the role of sRNAs in sperm. In this study, male mice (F0) were divided into two cohorts: a stress group (F0-Dep) exposed to daily unpredictable mild stress for a period of five weeks, and a control group (F0-Ctl) that was unexposed. Behavioural assays showed that

F0-Dep mice exhibited depressive-like symptoms, including weight loss and reduced sucrose intake. Physiologically, F0-Dep mice also had elevated corticosterone levels, a hormone analogous to cortisol in humans, and increased expression of corticotropin-releasing hormone (CRH) mRNA in the hypothalamic paraventricular nucleus (PVN). These markers are consistent with hypothalamic-pituitary-adrenal (HPA) axis hyperactivity and depression.

The study then examined whether these depressive-like traits could be inherited by offspring. Both the F0-Dep and F0-Ctl males were mated with healthy females, producing F1-Dep and F1-Ctl offspring. At baseline, both offspring groups showed similar behavioural profiles. But, after two weeks of mild stress exposure, the F1-Dep offspring displayed depressive-like behaviours similar to their fathers. F1-Dep had overexpression of CRH mRNA in the PVN, and dysregulation of mRNAs for glutamate receptors, synaptic proteins, and neurotrophic factors in the hippocampus and medial prefrontal cortex (mPFC). These results were confirmed by immunoblotting analysis of proteins, and genome-wide RNA sequencing to describe general transcriptome alteration patterns between parental groups and their offspring. Neural activation and synaptic transmission were assessed by a c-Fos immunochemistry marking technique, which highlighted increased activation of CRHergic neurons (indicating HPA axis activity) and decreased neural activity in the hippocampus and mPFC associated with depression as seen in Figure 2 (Wang et al., 2021).

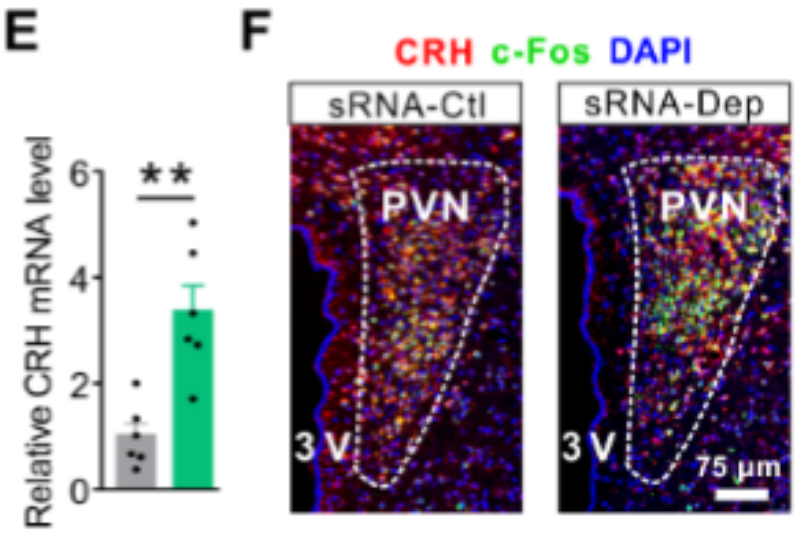

Figure 2. **Sperm sRNA contributes to paternal transmission of depression-like symptoms.** E) The graph shows that there is more than three times the level of corticotropin-releasing hormone (CRH) mRNA expression in the F1-Dep mice (indicated by the green bar) when compared to F1-Ctl mice. F) The increased activation of CRHergic neurons in F1-Dep mice (sRNA-Dep) is indicated by the highlighted green fluorescent regions by c-Fos immunochemistry when compared to the F1-Ctl mice (sRNA-Ctl).

To isolate the potential role of sperm RNA in transmitting these phenotypes, Wang et al. extracted and purified sperm RNA from F0-Dep and F0-Ctl mice. They injected this RNA into zygotes, which were then implanted into surrogate mothers. Interestingly, when only sRNAs from F0-Dep sperm were injected, the resulting offspring displayed depressive-like phenotypes, whereas long RNAs (lRNAs) alone did not reproduce these traits. Through RNA sequencing, the authours identified 19 differentially expressed microRNAs (miRNAs) in F0-Dep sperm, which were then synthetically reproduced and injected into zygotes, resulting in depressive markers in offspring. Furthermore, the use of antisense oligonucleotides to neutralize these miRNAs in zygotes eliminated depression-like phenotypes, suggesting that sRNA transmission from sperm

was essential for the inheritance of depressive-like traits. Notably, this effect was intergenerational rather than transgenerational (Wang et al., 2021).

Finally, Wang et al. (2021) were able to describe a possible mechanism for epigenetic inheritance through a secondary mechanism. The early embryonic period is a critical window of plasticity for developing the adult phenotype. To investigate this, miRNA from both F0-Dep (stressed) and F0-Ctl (control) mice were directly injected into zygotes and changes in gene expression were examined. They found that 264 embryonic genes were differentially expressed in embryos injected with miRNA from F0-Dep mice, with 78 of these genes directly targeted. Six key proteins (App, TSpan2, Wnk3, Ly6a, Grin3a, and βCamKII) were analyzed using a luciferase reporter assay to confirm miRNA binding at the 3' untranslated regions of their mRNA. This binding reduced the expression of five of the proteins, while βCamKII expression was upregulated. These miRNA-induced changes suggest that the paternal transmission of depressive phenotypes in mice involves disrupted neuronal development and function during early embryonic stages (Wang et al., 2021).

Gapp et al. (2018) Study and Findings

Gapp et al. (2018) investigated the role of both sRNAs and lRNAs in the epigenetic inheritance of trauma-related phenotypes. Using a different model of stress, male mice (F1) were exposed to unpredictable maternal stress combined with maternal separation (MSUS) shortly after birth. This generated a trauma-induced phenotype. As adults, these MSUS mice exhibited behavioural and metabolic changes, including altered food intake, glucose response, and risk-taking behaviour. Sperm from MSUS males were collected, and RNA was purified, yielding both sRNA and lRNA fractions. Gapp et al. then used these purified RNA samples to assess their phenotypic impact on offspring. They injected fertilized oocytes with either total RNA, only

sRNA, or only lRNA from MSUS males, while unexposed male sperm RNA was injected into a control group (Ctl F1). Figure 3 shows the experimental processing of two groups of mice.

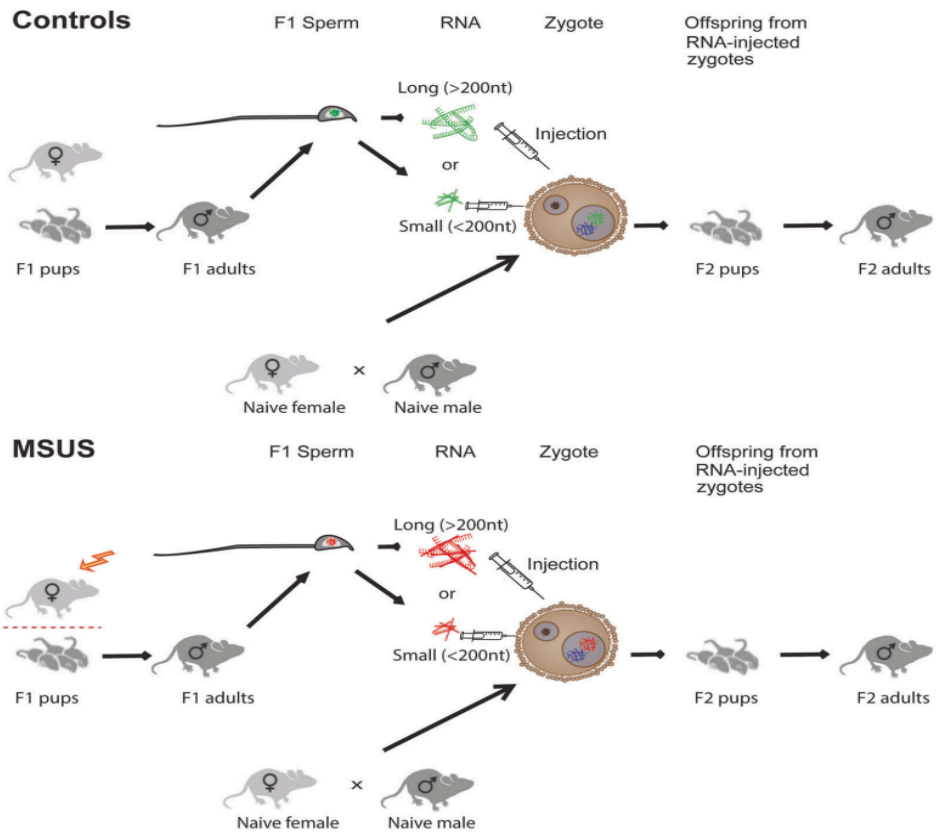

Figure 3. **Generation of study and control group for mice.** F1 male mice are generated from both control and MSUS (maternal separation with unpredictable stress) conditions. From postnatal days 1 to 14, MSUS mice undergo unpredictable maternal separation and stress, while control mice are left undisturbed. Once they reach adulthood, sperm is collected from both MSUS and control males, and RNA is extracted. This RNA, including both long (>200 nt, like mRNA and lncRNA) and small (<200 nt, like miRNAs), is size-selected for use in zygote injections. The RNA is injected into naïve fertilized oocytes, which are then implanted into foster mothers to produce offspring.

Results showed that sRNA injections produced alterations in body weight and behavioural despair in the offspring, similar to the findings from Wang et al. (2021). Behavioural

despair is measured by the amount of time a specimen is immobile during a forced swim test. However, Gapp et al. found that injecting lRNAs induced additional phenotypes in offspring, including changes in food intake, glucose metabolism, and risk-taking behaviour. Transcriptomic analysis further revealed upregulation of transposable elements in F1 sperm, which may have regulatory effects on gene expression during spermatogenesis. Interestingly, the trauma-induced phenotypes observed by Gapp et al. were transgenerational because they persisted across three generations. This transgenerational effect suggests that lRNAs or perhaps total sperm RNA is necessary in maintaining epigenetic changes in response to trauma, with potential implications for the stability and inheritance of complex stress-induced traits.

Discussion: Comparing Wang et al. (2021) to Gapp et al. (2018) and Implications

Both studies provide critical insights into the epigenetic inheritance of stress-induced phenotypes via sperm RNA, yet they highlight different mechanisms and outcomes. Wang et al. (2021) emphasize the role of sRNAs, specifically miRNAs, in mediating depressive-like behaviours, showing that sRNAs alone are sufficient to replicate paternal depression phenotypes in F1 offspring. This inheritance is temporary, disappearing by the F2 generation, suggesting that sRNA-mediated effects may be limited to a single generation. In contrast, Gapp et al. (2018) found that both sRNAs and lRNAs contribute to the transmission of trauma-induced phenotypes. Unlike the intergenerational effect found by Wang et al., the transgenerational effect in Gapp et al.'s study persisted across multiple generations, suggesting a more stable epigenetic mechanism facilitated by total RNA populations in sperm.

Additionally, a study by Dickson et al. (2018) was able to compare miRNA expression in the sperm of male mice and adult men. The authours isolated sperm RNA from male mice who were either exposed or unexposed to postnatal stress as well as adult men who took an Adverse

Childhood Experience (ACE) questionnaire. Incredibly, quantitative polymerase chain reaction (PCR) analysis revealed an inverse relationship between miRNA from the 34 and 449 family and ACE scores: adult men with high ACE scores, indicating childhood trauma, had up to 300-fold reductions in the expression of these miRNAs. This relationship was also observed in mice that were exposed to stress compared to those that were not. In other words, both human and mice males that have been exposed to stress or adverse trauma showed altered expression of sperm miRNAs that function to critically regulate brain development and spermatogenesis (Dickson et al. 2018).

Correlation Studies

Heritability of PTSD from Holocaust Survivors

Correlation studies are creative ways to jump-start research in the field of epigenetic inheritance. Correlation studies act as a building block for future research into the specific mechanisms that result in the inheritance of epigenetic modification due to trauma. A study done by Yehuda et al. (2016), focused on intergenerational effects on FKBP5 methylation in Holocaust survivors and their offspring. The FKBP5 allele is a co-chaperone protein (Pan et al., 2021) that binds and inhibits glucocorticoid to its report. The activity alterations of the glucocorticoid receptor is associated with PTSD and other major depressive disorders (Yehuda et al., 2016). Methylation of cytosine-phosphate-guanine (CpG) at six different sites was looked at specifically on intron 7. Intron 7 is in direct physical contact with the FKBP5 transcriptional start site and the methylation of this site therefore affects FKBP5 gene expression (Yehuda et al., 2016). The major comparison of this study was comparing intron 7 from peripheral blood samples of Holocaust survivors to a demographically matched Jewish control population that represents the

offspring of the Holocaust survivors. The study only looked at five groups of Holocaust survivors and their biological offspring. The lack of direct biological offspring of Holocaust survivors outlines another gap in inheritable epigenetic research that this study tried to work around.

To decipher if conditions like PTSD are heritably passed down due to different methylation of the FKBP5 gene a Childhood Trauma Questionnaire (CTQ) was conducted on all participants. The results of this questionnaire helped to show the correlation of different traumatic experiences and differential methylation specifically on intron 7. It was found that physical and sexual abuse caused significant methylation changes on intron 7 in bin 2. It was also found that in bin 3 at site 6 of intron 7, methylation of CpG methylation differed and it is predicted to be due to parental exposure (Yehuda et al., 2016).

Intergenerational Trauma in Indigenous Populations Resulting in Obesity

The influence trauma has on different cultures is an expanding area of research to help understand long-term epigenetic influences. In particular, the trauma faced by many Indigenous communities In Canada, the United States and Australia have been a key area of research. Trauma can come in many different forms, the article by Schafte and Bruna (2023), focuses on the impacts of historic and intergenerational trauma in Indigenous communities. Historic trauma helps to understand the psychological and social issues of these communities, while intergenerational trauma can help relate issues back to epigenetic changes during pregnancy. Many indigenous communities have faced a long history of trauma involving oppression, discrimination, systematic racism, and colonialism, which has all impacted their traditional ways of life. We are now realizing it is continuing to impact their health (Schafte & Bruna, 2023). Currently, Indigenous communities are facing an increase in health concerns like obesity.

Obesity is an epigenetic disease (Schafte & Bruna, 2023) and the expression can be affected during embryogenesis. It has been found that expression of genes responsible for placental, embryonic and fetal growth as well as adiposity and energy metabolism are affected. Improper expression of these genes has been found to result not only in obesity but also in hypertension, insulin resistance, diabetes, stroke and coronary heart disease (Schafte & Bruna, 2023).

Trauma has a strong link to nutrition; malnutrition, poor health choices, overeating, and a loss of traditional health practices has resulted in conditions like obesity and is passed down both epigenetically and behaviourally (Schafte & Bruna, 2023). Many parents who experienced trauma in the past have shown many behavioural changes that impact their children and grandchildren. One example is the idea of feeding as a form of love and expressing culture. Indigenous people forced to attend residential schools and the children of these survivors, had their culture stripped from them and repressed throughout their life. To compensate for their intergenerational trauma, they try to show their love through food which has resulted in overeating and obesity in the children and grandchildren of many Indigenous communities. Another study on people who attended residential school, found that traumatic stress is also passed down epigenetically. The study based their findings off of an allosteric load scale. Allostasis is how the body deals with stress and allosteric load is the forced adaptation to adverse psychosocial or physical situations. The allosteric load scale was based on specific biomarkers for obesity (Schafte & Bruna, 2023). In the study reviewed by Schafte and Bruna, it was found that the increase in the offspring's allosteric load was more so due to the material experience in residential school and not due to external behaviours as the child grew up. It was also found that the offspring of mothers who attended residential school were five times more likely to have

high-mid allosteric load level compared to offspring mothers who did not attend (Schafte & Bruna, 2023).

Lastly it is important to note that this study mentions how future research in the area of epigenetics due to trauma, and the ability for that to be passed down to offspring must be addressed in a particular way that does not put the blame onto the people who experienced the trauma. As a society we are still facing the issues of historic trauma and it is unethical to present any finding on trauma inheritance in a way that blames the mothers for the health of their child. This outlook diminishes the responsibility of society to solve the issues and instead blames the people who have been through traumatic experiences that were out of their control.

Conclusion

To summarize, the ways in which trauma can affect future generations through epigenetic pathways is a multifaceted process. Understanding the role of epigenetic transmission in the genome, and especially how higher-order eukaryotes may inherit these modifications requires more functional and longitudinal studies to investigate transgenerational effects (Fitz-James & Cavalli, 2022). Importantly, we have described studies that show how trauma can induce inherited epigenetic modifications through the primary method of DNA methylation, and the secondary method of sperm RNA.

The findings from Pilkay et al. (2024) and Broeks et al. (2023) suggest that early childhood trauma of the maternal parent has direct epigenetic links to the gene expression displayed by their offspring via alterations in DNA methylation. Interestingly, Pilkay et al. (2024) reported specific pathways are activated depending on which parent was abusive,

displaying unique gene expression that may have some differences and similarities depending on the sex of their child.

Studies on sperm RNA by Gapp et al. (2018) and Wang et al. (2021) suggest that different RNA types may work independently or in unison to influence phenotypes across generations. Further studies could investigate how these mechanisms interact and whether they might help explain how inherited stress and trauma affects humans. Specifically, how it might affect the development or predisposition of various pathophysiological diseases and psychological disorders (Gapp et al., 2018).

In the correlation studies, it is evident that more primary research must be done to determine the exact pathways that are modified and if these epigenetic modifications can be passed down through multiple generations. However, there is strong evidence that suggests that intergenerational trauma is related to obesity, PTSD, depression and anxiety through both behavioural and epigenetic pathways. It is difficult to determine the mechanisms of the epigenetic pathways and inheritance of these changes due to the complexity of DNA methylation and histone modifications, and because many of these studies take a more psychiatric approach than a genetic approach. This review has identified, through the investigation of murine and human models several effects of inherited epigenetic traits due to trauma.

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