Intergenerational Epigenetic Effects of Parental Trauma on Offspring

Phoenix S. Bryant

Takoma Park/Silver Spring Montgomery College

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Professor Jurata

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Abstract

Intergenerational trauma is a topic that is relevant in the context of history and today. It is mostly thought of by the general public as something that is inadvertently taught by parents to children from an early age and exacerbated by systems we have in place today, such as systematic racism and poverty among other things. Recently there has been evidence for a deeper, biological, reason for parental trauma passing on to offspring: Epigenetics. Epigenetic changes due to parental stress can be inherited by offspring resulting in phenotypic changes that are not due to the child's environment, but biology. This review examines the role of DNA methylation of the FK506 binding protein 5, a gene that negatively regulates the stress pathway, and microRNA in sperm in the intergenerational transmission of epigenetic changes caused by parental trauma.

Introduction

Epigenetics is the study of behavioral and environmental factors and their effect on how DNA is read, and how the genes work (Centers for Disease Control, 2022). It was previously thought that the trauma experienced by a parent affected the way the child was raised, and therefore their behavior, because children can infer the traumas of their parents through their parent's tone and emotion (Hughes, 2021; Shulevitz, 2014). New evidence suggests that chronic stress or childhood adversity results in the intergenerational transmission of psychopathologies due to epigenetics, and that the children of those traumatized parents, may not be as equipped to metabolize stress as compared to other people (Jawaid et al., 2021; Shulevitz, 2014).

Epigenetic modifications can be caused by multiple mechanisms including DNA methylation, histone modification, and non-coding RNAs like microRNA (miRNA). DNA methylation works by adding a methyl group to a certain place on the DNA, and blocks where the proteins would attach to the gene to help express it. Methylation is a light switch for the gene, when it is unmethylated, the gene is turned on, and when it is methylated, the gene is turned off (Centers for Disease Control, 2022). Histone modification is when the DNA is too tightly wound around the protein called a histone, making it so the gene is turned off, whereas the unwound DNA is considered turned "on," thus gene expression can be turned on or off by adding or taking away chemical groups on histones (Centers for Disease Control, 2022). Epigenetic modification can also involve non-coding RNAs. Coding RNA codes for proteins through instruction from the DNA, but non-coding RNA attaches to a coding RNA to control gene expression by making the coding RNA unable to make proteins (Centers for Disease Control, 2022).

One way that intergenerational trauma can be passed down epigenetically appears to be through methylation of the gene that codes for FK506 binding protein 5 (FKBP5). FKBP5 is

related to the stress response pathway in the body and negatively regulates or inhibits the glucocorticoid receptor (GR), which is a receptor for stress hormones like cortisol (Thumfart et al., 2022). The GR can detect the high cortisol levels and help the body adapt to stress by affecting expression of many genes (Thumfart et al., 2022). Another critical component in the stress pathway is the hypothalamic-pituitary-adrenal (HPA) axis, which results in the production of cortisol. The HPA axis is found to be hyperresponsive after chronic stress or childhood trauma (Thumfart et al., 2022). Therefore, demethylation of the FKBP5 gene results in decreased ability to cope with stress because FKBP5 expression is increased and there is a dampening of the negative feedback loop of the HPA axis.

Another crucial factor in passing on phenotypic changes epigenetically to offspring is the role of non-coding RNA. Gametes carry miRNA, which are non-coding RNAs, and those miRNAs could potentially affect offspring produced by the gametes by translating the epigenetic changes of the parent to offspring. Before it was thought that in your gametes, the slate got wiped clean metaphorically, but now research supports miRNA in sperm as one of the mechanisms by which phenotypic changes can be inherited by offspring (Rodgers et al., 2015).

In this review, the phenotypic changes in offspring due to the parent's childhood adversity, abuse, post-traumatic stress disorder (PTSD), and war are discussed. The evidence from the assorted studies shows that trauma and stress cause epigenetic changes that can be inherited by the next generation through methylation of genes such as FKBP5 and through miRNA in sperm. Thereafter, these epigenetic changes cause stable phenotypic changes in offspring which can potentially affect the offspring's survival, depending upon the situation in which they are born.

FKBP5 methylation and intergenerational trauma

FKBP5 methylation in Holocaust survivors and their children

Rachel Yehuda (2016) and her team have done numerous studies on the intergenerational epigenetics of trauma and PTSD. In one study the intergenerational effects of the Holocaust on FKBP5 methylation in Holocaust survivors and their offspring were examined by sodium bisulfite mapping of DNA from blood samples. DNA methylation of the FKBP5 gene, more specifically in intron 7 was studied, because that gene is linked to the stress response. The wake-up cortisol in the affected parents and their children was also measured. The researchers did the same to a demographically similar, i.e., Jewish, control group who were outside of Europe during World War II, and their children. Compared to the control group, affected parents and their offspring showed altered methylation of the FKBP5 gene at the same site, just inversely, with the affected parents having a higher degree of methylation than the control group and the children having a lower degree of methylation than the control group (Yehuda et al., 2016). The study was done in such a way that the change in methylation could only be related to the experiences of the parent who witnessed the Holocaust because the control group was so demographically similar to the affected group (Yehuda et al., 2016). The functional aspect of the DNA methylation can be observed in the wake-up cortisol levels of the Holocaust survivors and their offspring. A negative correlation was found between wake-up cortisol and FKBP5 methylation at that specific site; the offspring of the Holocaust survivors with the higher the degree of methylation showed a lower concentration of cortisol (Yehuda et al., 2016).

This study suggests that epigenetic changes in parents who experience traumatic events might be passed on to the children to prepare them for traumatic events (Yehuda et al., 2016). The demethylation of the FKBP5 gene in the offspring allows for higher concentrations of

cortisol and the inhibition of GR, which would suggest a worse coping mechanism with stress, but could be useful if the offspring were placed in that same situation (Yehuda et al., 2016). Cortisol would always be available for facilitating the flight or fight response in the children (Rodriguez, 2015). These intergenerational epigenetic changes allow for adaptation in offspring should they be born in those same unsavory conditions, and improve the survival of offspring. However, intergenerational effects could potentially cause psychopathology in the survivor's offspring who no longer need these adaptations because they grew up after the Holocaust ended (Yehuda et al., 2016). Further study of the detection of epigenetic markers could allow for therapies and treatments to be developed to deal with effects of intergenerational trauma (Yehuda et al., 2016). Investigation is also required to elucidate the specific mechanism by which DNA methylation was transmitted intergenerationally, through the gametes (Yehuda et al. 2016). Treatment options could also be explored. Gene editing technology could potentially be used to change the epigenome and therefore reverse the epigenetic effects of the exposure to trauma, as well as more standard treatments such as medication with antidepressants.

FKBP5 methylation in infants

Another study looked at FKBP5 methylation in pregnant women who experienced adversity in their adulthood or childhood, or PTSD, and their newborn infants (Grasso et al., 2020). FKBP5 intron 7 methylation was observed in this study as well using bisulfite sequencing. The saliva of the women and the infants were swabbed within 24 hours of birth to look at methylation of the FKBP5 gene. The mother's history of adverse childhood experiences, PTSD, and adult trauma was linked to decreased methylation of FKBP5 (intron 7) and increased methylation in the infants compared to a demographically similar control group (Grasso et al.,

2020). This is different from the Yehuda (2016) study in that the roles were switched. These conflicting results could be due to the distinct types of traumas that adverse childhood experiences produce versus the traumas of the Holocaust. The fact that the newborns were swabbed within 24 hours of birth is important because they have not had a chance to live life yet with their mother so parenting nor life in general for the child could affect the methylation of FKBP5 yet (Grasso et al., 2020). These findings suggest that the infants developed an adaptation to blunt the effects of stress which could be advantageous for an infant going into a situation like their mother (Grasso et al., 2020). This study has some shortcomings in that it does not investigate the relationship between the levels of cortisol and methylation in the mothers and infants which would provide a physiologically relevant example of how the methylation translates into a phenotype that might be advantageous for the offspring. The study also does not follow the infants developmentally to see how methylation changes over time (Grasso et al. 2020).

The Grasso (2020) study provides an interesting insight into offspring epigenetics from a much earlier developmental period compared to the offspring from the Yehuda (2016) study on Holocaust survivors, in which adult offspring were examined. Even though some results conflict with Yehuda's (2016) study, the Grasso (2020) study further supports methylation of the FKBP5 gene as a mechanism for passing down stress-related epigenetic processes from parent to offspring.. It would be beneficial to see how methylation patterns of infants with mothers who had experienced war and genocide would compare to Yehuda's (2016) study to see if the results in methylation would be more similar to this one or Yehuda's.

Micro-RNA in sperm passing down epigenetic traits

The role of DNA methylation in stress-related pathways in somatic cells has been studied, but what about the gamete? Life produced sexually begins with two gametes, the egg, and the sperm, to form a zygote. This zygote then goes on to grow to be an infant, like those studied in Grasso's study (2020). Presumably, epigenetic reprogramming occurs in the embryo to give offspring the best chance for survival by the egg and sperm "learning" from the experiences of the parents. The involvement of the gamete in the intergenerational epigenetics of trauma was studied by Rodgers (2015) and his team looking at the involvement of miRNA in sperm and how that translates into the intergenerational passing down of epigenetic traits that were caused by stress. In the experiment, male mice were exposed to chronic stress. This resulted in a blunted HPA stress axis response, meaning that the mice did not respond to things that make other mice nervous. Nine specific miRNAs of their sperm were isolated and placed in a zygote made from a healthy female and male mouse, and then the offspring were raised normally by the mother (Rodgers et al., 2015). The multi-miRNA injected group showed lower cortisol compared to the control group of mice, which were injected with a phosphate-buffered saline (PBS) solution or the group with a control miRNA injected (Rodgers et al., 2015). Interestingly, the multi-miRNA injection also affected the expression of some mRNAs stored in the egg, resulting in those mRNA being reduced to as little as one quarter of the control levels (Rodgers et al., 2015). These results point to the effect of miRNA from the paternal line affecting the HPA axis reactivity in the offspring and show how miRNA in sperm can affect zygote development in the targeted reduction of expression of maternal mRNAs (Rodgers et al., 2015). This experiment provides insight into how parental trauma-related epigenetic markers might be established in embryo, and how these changes might help to prepare the offspring for a stressful life.

Potential for treatment

Encouragingly, there is evidence that environmental enrichment can reverse the effects of paternal trauma on the offspring. Gapp et al. (2016) kept male mice who experienced unpredictable maternal separation and unpredictable maternal stress (MSUS) in mildly adverse conditions and then exposed their male children to those same conditions. The mildly adverse condition was a brightly lit box, in which there was a dark box the mouse could escape to. Both the MSUS male and their offspring had a slower escape response possibly due to higher tolerance of adverse conditions passed down from father to child, hypothetically by epigenetic transmission through the gametes (Gapp et al., 2016). The researchers also observed a more active coping response in the MSUS males and their offspring during a different avoidance task in which the mouse's feet were shocked until it nose-poked a hole. The MSUS males and offspring were fastest to nose-poke compared to control mice in this experiment (Gapp et al., 2016). The MSUS males and their offspring were then exposed to environmental enrichment (a big cage with things to play with) and that resulted in normalization of behavior compared to the control mice (Gapp et al., 2016). Methylation of the GR gene was implicated in the behavioral changes in the mice (Gapp et al., 2016; Beras, 2017).

Conclusion

Whether it is massive stress in life like childhood adversity or war, the body will try to do everything it can to adapt to those changes and help potential future offspring adapt as well. The parent’s traumatic experiences can be passed down through epigenetic modifications, like DNA methylation, through the gametes of the mother and father which influence the epigenetics of the offspring. The life experiences of the parents, and their stress, results in methylation or

demethylation of the FKBP5 gene depending on the type of stress. Parents who went through the Holocaust showed more methylation and mothers who experienced childhood adversity showed less methylation than control groups (Yehuda et al., 2016; Grasso et al., 2020). Depending on which direction methylation in the parents went, the offspring showed the opposite pattern. Demethylation of the FKBP5 gene results in increased expression of FKBP5 in the offspring, which works as an inhibitor for the GR. These offspring have higher levels of cortisol resulting in the children always being ready to flee or fight which would be an important adaptation for children growing up in the Holocaust, but for offspring born in a time when being on high alert all the time is not necessary, this can possibly result in psychopathologies in the offspring like depression or anxiety (Yehuda et al., 2016). The Holocaust parents had higher methylation most likely due to the conditions the Holocaust put them in, like being starved, and the use of cortisol in those situations would not be advantageous because high levels of cortisol can shut down other processes like the immune system which is not useful for the parents to survive (Yehuda et al., 2016). So, the differences in methylation patterns were most likely due to the different types of traumas or length of trauma exposure of the mothers in Grasso's (2020) study versus the parents in Yehuda's (2016) study.

The role of miRNA in sperm in intergenerational epigenetics is also interesting because it shows stressed individuals may carry those epigenetic changes in their gametes through miRNA, and then pass on those changes to their children. It is possible that miRNAs influence sustainable epigenetic modifications like histone modifications, and DNA methylation changes. These result in changes to the phenotype of the children enabling adaptation to the challenging environment their parents experienced. More research is needed specifically on the intergenerational

transmission of trauma through the gametes of the mother and father and how this leads to more adaptable offspring.

Additionally, it would be interesting to investigate the transgenerational (across multiple generations) transmission of trauma through epigenetic markers and how those affect historically disadvantaged populations, like African Americans or Native Americans, today. In African Americans, transgenerational trauma stems from slavery and continues possibly to this day. For example, white adults having a better cardiovascular system than African American adults could be due to changes in the epigenome being passed down generation to generation due to historical and modern discrimination against African Americans in the U.S. (Conching and Thayer, 2019). Historical trauma could also build up in the form of stressors from generation to generation. For example, a Native American mother's hopelessness and stress that comes with having her land taken away could translate to epigenetic modifications that are then passed on to her children. Those children do not personally experience the tragic event, but the homelessness and poverty experienced by the parent(s) that comes with having land taken away by foreigners could result in epigenetic changes passed down to their kids, and so on and so on (Conching and Thayer, 2019). These epigenetic marks could lead to health or mental disorders in the descendants (Conching and Thayer, 2019). It would be interesting to see a study that follows methylation through multiple generations of descendants of a trauma-afflicted individual to see the effects of trauma on the epigenome throughout generations, such as the generations of offspring from children in third-world countries who were raised in orphanages (Curry, 2019).

These results may be scary to think about, especially if you have experienced trauma and want to have children or are the child of someone who has experienced trauma, but epigenetic markers can be reversible with treatment (Thumfart et al., 2022). Histone deacetylase inhibitors,

for example Trichostatin A, were shown to decrease DNA methylation on the rats that experienced barely any care from their mothers (Thumfart et al., 2022). More research is still needed to figure out how to reverse epigenetic modifications in humans, but recognition of the transmission of epigenetic markers due to stress from parent to child could increase the importance of identifying ways to reverse the changes.

In addition to research into ways to reverse epigenetic changes due to trauma and stress, recognition on the global scale of the importance of epigenetics in the transmission of trauma epigenetically may result in more rigorous screening for sperm and egg donors. If their childhood and adult experiences result in changes to the epigenome in gametes and therefore the zygote, these changes that could affect the child's response to stress. Hopefully, recognition of the role of epigenetics and its role in passing trauma intergenerationally with associated psychopathologies could reduce the stigma surrounding therapy and getting treatment for past trauma and stress.

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