Stress-induced Germline Epigenetic Inheritance: Determinants, Challenges, and Preventive Strategies

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Abstract— **The stress an individual experiences never affects only that person. This impact can also extend to their biological children. You may wonder how stress experienced by the previous generation can pass down to children through bloodlines? A growing number of studies have identified a key entry point to this question: in the human body's germ cells responsible for reproduction, namely sperm and eggs, there exists a set of information that does not alter the inherent sequence of DNA but can regulate the activation or silencing of genes—this is epigenetic information, specifically including DNA methylation, non-coding RNA, and chromatin structure. All these types of information can be altered by the environmental and psychological stress a person experiences. However, not all this stress-altered epigenetic information is naturally passed on to the next generation. Whether it can be transmitted is jointly influenced by several intertwined factors: first, the specific type of the epigenetic modification itself; second, which developmental stage the germ cell is in when these modifications occur; and a core condition, the epigenetic reprogramming mechanism that acts on these markers—the physiological process that erases most old epigenetic markers and resets the state for the new life during the development of embryos and germ cells. The combination of these factors determines whether the changes caused by stress can cross this erasure threshold and be passed on to children. This review collates all relevant current research, organizes the mediating factors that affect whether stress-induced germline epigenetic changes can be inherited, and discusses several potential intervention directions—blocking this transmission by adjusting nutrition, changing lifestyles, or using molecular methods—to minimize the impact of parental stress on children's health. Existing research still has many limitations: the models used in different experiments vary too widely, with inconsistent experimental animals, stress application methods, and detected indicators, so results cannot be arbitrarily combined and compared; previous findings obtained from experimental subjects such as animals lack support from human experimental data, and cannot be directly applied to humans; another long-unresolved problem is the inability to distinguish between intergenerational effects and true transgenerational epigenetic inheritance—in simple terms, it is impossible to tell whether a child's abnormalities are only directly inherited from their parents, or can actually be passed down to grandchildren or even later generations who never encountered the original stress. Based on these limitations, future research first needs to identify stable, replicable heritable molecular changes, confirm which changes can truly cross the reprogramming threshold and be passed down through generations, and then develop effective, accessible intervention methods to reduce the impact of parental stress on offspring.**

Keywords—**stress, germline, epigenetic inheritance, transgenerational inheritance, preventive strategies**

I. Introduction

People living in the world inevitably encounter various environmental pressures. These stresses fall into two categories: one is sudden acute shocks, and the other is long-term chronic burdens, such as persistent psychological anxiety, major trauma experienced in life, physical metabolic disorders, or exposure to other harmful factors in the environment. Each type can cause tangible harm to health. These stresses not only disrupt the normal rhythm of neuroendocrine function, impair the body's metabolic capacity, and alter an individual's daily behavior, but can even reduce fertility. Beyond this, a growing number of studies have found that they leave longer-lasting chain effects—first altering the epigenome in parents' germ cells, then through the transmission of germ cells, causing health problems in offspring, an impact that can span multiple generations.

Many recent animal studies have identified specific pathways of this impact: if a child's father experiences psychological stress or trauma during the preconception period, or after the child's birth, this directly changes the DNA methylation pattern and RNA distribution in that father's sperm [1]. After a sperm carrying these changes combines with an egg to form an embryo, the child ultimately born may develop various behavioral, metabolic, or physiological abnormalities. A core

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question lies beneath this phenomenon: the environmental harm experienced by the previous generation never modified the offspring's DNA sequence, so why are offspring who never even encountered the original stress affected by it?

Currently, the most widely discussed explanation is a series of mechanisms of epigenetic regulation. This mechanism is completely different from the gene mutations we commonly refer to—gene mutations permanently alter the nucleotide sequence of DNA, equivalent to rewriting the underlying genetic code, while epigenetic modifications only adjust the activity and expression level of genes, equivalent to only switching genes on or off and adjusting their gear, without altering the core genetic code itself. The core biological pathways supporting epigenetic regulation are four: DNA methylation, histone modifications, non-coding RNA molecules, and chromatin remodeling. Environmental stress can disrupt these pathways in germ cells, causing these regulatory mechanisms to malfunction. Subsequently, sperm carrying this altered epigenetic information enter a fertilized egg, forming a solid biological link that connects the father's personal experiences to the child's lifelong developmental trajectory.

However, one point must be clarified first, and must never be confused: the presence of epigenetic changes in germ cells does not equate to the occurrence of true transgenerational inheritance. Two completely distinct concepts must first be distinguished: intergenerational effects and transgenerational inheritance. Intergenerational effects refer to situations where the original stress directly affects the person who experienced it, or the generation that was developing and bound to the individual at the time. For example, if a father experiences stress and his F1 generation, that is, his direct offspring, develops health problems, this counts as an intergenerational effect—the changes in this F1 generation are directly tied to the exposure of the father's generation. True transgenerational inheritance, by contrast, requires evidence that generations that never directly encountered the original environmental stress also develop health problems. Precisely because the boundary between the two is so clear, observing physiological changes only in the F1 generation is completely insufficient to prove that transgenerational epigenetic inheritance has occurred.

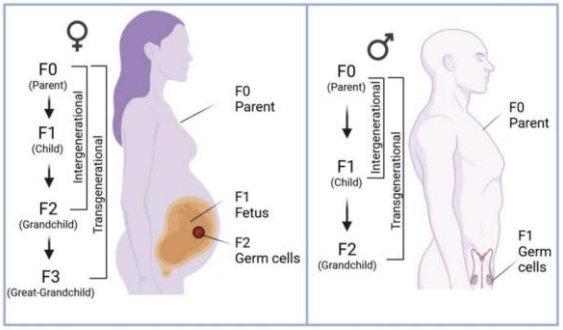


Fig. 1. Distinction between intergenerational and transgenerational effects following parental exposure.

A core unavoidable challenge in this field is that during the development of germ cells and the formation of early embryos, a genome-wide epigenetic reprogramming is initiated—put simply, it performs a global "reset and cleanup" of epigenetic markers in germ cells and embryos. This process erases the vast majority of epigenetic markers, leaving only a clean set of initial regulatory signals for the new life's development. Even though most markers are cleared, some stress-induced modifications can persist, or even reappear after reprogramming ends. However, the molecular mechanisms that support these modifications in evading cleanup and maintaining stability have not yet been clarified. Most existing studies have focused on DNA methylation and non-coding RNA, and have collected relevant data from animal models and human samples, but the claim that these stress-borne epigenetic markers can achieve transgenerational inheritance has never been definitively confirmed in human populations.

This leads to a core urgent question: what core conditions must stress-induced epigenetic alterations meet to become stable heritable traits? The analysis in this paper breaks down four decisive foundational factors: the type and stability of the epigenetic alteration itself, the developmental stage the germ cell is in when reprogramming occurs, the molecular regulatory mechanisms that can stabilize new regulatory patterns, and the combined effect of stress characteristics and the host's own characteristics.

II. Factors Determining the Heritability of Stress-Induced Germline Epigenetic Modifications

Not every change stress causes in germ cells persists and is passed down from generation to generation. You can understand it this way: not all traces stress leaves in germ cells can be retained as cells reproduce; only a very small portion can ultimately become transgenerational traits, while most gradually disappear during development.

For these epigenetic changes to be transmitted across generations, they must first occur in germ cells. This basic condition cannot be bypassed—if the change does not appear in germ cells responsible for inheritance, such as sperm or eggs, there is naturally no question of passing it to the next generation. Beyond this, another key condition must be met: they must either withstand the natural reprogramming that occurs during development, or be stably replicated during cell division. During the process where germ cells develop into embryos, the body has its own built-in reset mechanism, the reprogramming mentioned here, which erases most old epigenetic markers to give the new life a clean initial state. Only changes that pass this checkpoint have the possibility of being passed on further.

Whether these changes can be passed down from generation to generation is determined by a set of interrelated factors. It is not enough to meet only one or two of the previously mentioned conditions; from the timing of the change's occurrence to the nature of the change itself, to the body's regulatory mechanisms, and

even the characteristics of the stress itself, every link affects the outcome, and no single condition can determine the result alone.

A. Epigenetic Modification Types and Stability

Whether an epigenetic modification can transmit the impact of a previous generation's experiences to the next generation first depends on what type it is and how stable it is—this is an innate condition written into its molecular properties, which directly determines its potential for transgenerational inheritance. Currently, the epigenetic modifications we commonly discuss fall into four main categories: DNA methylation, histone modifications, non-coding RNA, and chromatin state. The molecular properties of these four types of modifications are fundamentally different, and the body's regulatory methods for them are also completely different throughout the entire process from the development of germ cells, i.e., sperm and eggs, to embryo formation [2–5].

Among all these modifications, DNA methylation is currently the core research direction for how stress triggers germline epigenetic changes. Its mechanism of action is simple: it adds markers to specific regions of the genome, altering the region's activity during transcription, that is, the synthesis of gene products, to regulate whether that gene functions. Numerous studies have found that external environmental stress can directly change the DNA methylation distribution pattern in sperm, but not all stress-induced methylation changes can be successfully passed to offspring. For example, Zheng *et al*. [1] found if a father experienced psychological stress, many regions in his sperm would have methylation levels different from the average person, what is professionally called differential methylation regions, abbreviated as DMRs. However, only a small portion of these changes can survive the various stages of embryonic development after sperm fertilization and be passed on to later generations. This result precisely illustrates that whether a methylation change can be inherited depends not only on whether it occurs in sperm, but also on whether it can withstand the genome-wide epigenetic reprogramming during embryonic development—the global reset the body performs on the embryo's epigenetic markers; only changes that are not erased have the chance to be passed down further.

Beyond the reprogramming checkpoint, the specific location of DNA methylation in the genome also greatly affects whether it can exist stably and not be easily erased. Some special regions of the genome are protected by dedicated regulatory mechanisms that can evade that genome-wide epigenetic reset. These mechanisms preserve specific epigenetic markers that need to be retained intact during development, and even if some markers are accidentally erased, they can be restored. Precisely because of these differences, DNA methylation at different locations across the genome varies widely in stability; whether it can persist depends entirely on the local genomic environment of its location and whether it has that special protective mechanism.

In addition to DNA methylation, histone modifications are also key carriers of epigenetic information. Histones are core proteins that wrap around DNA, and they themselves can undergo modifications such as methylation and acetylation. These modifications further alter the overall structure of chromatin, the complex formed by DNA and histones, ultimately regulating whether a gene can function normally. Scientists used a model organism called Caenorhabditis elegans, also known as the nematode worm, for research and found that histone modifications, and the enzymes responsible for making these modifications to histones, can truly pass epigenetic traits down from one generation to the next. In particular, histone methylation is also associated with the cell's process of remembering environmental stress, and can preserve the gene regulatory state related to stress intact [6]. Even with this research evidence, the duration that transgenerational inheritance achieved through histone modifications can be maintained is not fixed—the results vary across different species and different experimental conditions. This illustrates that not all histone modifications have the same stability; only a specific small subset of modifications, under specific conditions, truly participate in the process of transgenerational inheritance.

Non-coding RNAs such as Small RNAs that are not translated into proteins, along with other regulatory RNA variants, have opened up a completely new path for environmental signals to be passed to the next generation through germ cells. Sperm themselves carry a large number of RNA molecules used to regulate gene activity. After fertilization occurs, these RNAs enter the fertilized egg along with the rest of the sperm's contents, initiating the subsequent developmental process.

A study specifically observed cases where fathers had experienced trauma and found that changes in long RNA in sperm were clearly associated with traits that appeared in offspring; another experiment directly artificially modified sperm RNA, ultimately confirming that these types of RNAs do participate in the transmission of trauma's effects across generations. Similarly, sperm-derived small RNAs linked to a father's stress can interfere with normal molecular activities in early embryos, ultimately altering the traits of offspring. These research conclusions all point to one fact—non-coding RNAs in germ cells actively participate in the process of passing the environmental information a father was exposed to his offspring.

This intergenerational transmission of information achieved by RNA operates according to a completely different logic from inheritance achieved by DNA methylation. RNA itself is a constantly changing, active molecule—cells continuously synthesize new RNA and degrade old, useless RNA; its activity is also regulated by the body at all times. In addition, different RNAs have different quantities in cells and different target sites they can bind to. This leads to the stability of non-coding RNAs and whether they can be successfully passed to the next generation, depending on two conditions: what type

of RNA it is, and which developmental stage the organism is in when it exerts its effect [7–10].

In addition to RNA and DNA methylation, chromatin structure, and whether it can be accessed by transcription-related proteins, that is, transcription accessibility, also affects the transmission of epigenetic inheritance. Chromatin state is closely linked to the previously mentioned DNA methylation, histone modifications, and regulatory RNAs. However, chromatin remains dynamically changing in germ cells and early embryonic cells, and current research is far less clear on whether its stable state can be continuously passed to offspring, compared to research on DNA methylation or RNA-related mechanisms.

Different epigenetic modifications naturally vary in the duration they can persist and their ability to complete intergenerational transmission. Although the molecular type of the modification is a core factor affecting inheritance, no single epigenetic mechanism can fully explain the phenomenon of stress-induced transgenerational inheritance. On the contrary, whether this type of inheritance can occur depends on the dynamic, context-dependent interaction between the modification itself and the environment that induced it [3, 11–13].

B. Germ Cell Developmental Window

Whether stress-induced epigenetic changes in germ cells can be successfully passed to the next generation, the most critical influencing factor is which developmental stage the germ cell is in when the stress occurs—that is, the critical developmental window we refer to. The role of this window is more critical than many people realize. During the process from the initial growth of germ cells to their maturation, they undergo the first large-scale epigenetic reprogramming, equivalent to the cell performing a major cleanup on itself; after sperm and egg combine to form a fertilized egg, the early embryo will undergo another identical round of reprogramming. Under normal circumstances, these two cleanups completely erase almost all old epigenetic markers, preventing these previous generation's markers from being carried over to the next generation.

These two full-coverage cleanups are the biggest obstacle for environment-induced epigenetic changes that want to achieve transgenerational inheritance. Most modification changes stress leaves on germ cells will be erased in these two cleanups, with no chance of being passed to offspring. For a change to truly affect multiple subsequent generations, it only has two possible paths: either evade erasure and hide during the reprogramming cleanup, or, even if it is erased, it can reappear at a specific developmental node. This situation of persisting or reappearing is rare, but it has been recorded in research and is the core foundation for the validity of transgenerational epigenetic effects.

Zheng *et al.* [1] conducted a set of experiments using mice, exposing male mice to long-term psychological stress to construct a model of paternal chronic psychological stress, which exactly reproduced this special dynamic process. They tracked the changes in stress-related DMRs in sperm, that is, differentially methylated regions, throughout the entire embryonic development stage. The study's results were completely consistent with previous inferences: a set of DMRs that ultimately could be stably inherited by offspring temporarily disappeared during the reprogramming cleanup phase, then reappeared later in embryonic development. This pattern precisely points to the potential mechanism supporting the stable transgenerational transmission of epigenetic inheritance, and confirms the core role of the developmental window—the timing of stress exposure not only determines whether an epigenetic marker can form on a germ cell, but more importantly, whether it can successfully pass through the two rounds of reprogramming cleanup, and truly affect the offspring of the person who experienced the stress.

The key impact of the timing of stress occurrence actually runs through all stages of germ cell and embryo growth. If a germ cell encounters environmental stress while it is actively differentiating and its own epigenetic markers are still being adjusted and remodeled, this will directly disrupt the originally normal core epigenetic programming process; even if stress is encountered after adulthood, when germ cells are fully mature, it can leave long-lasting markers in fully formed sperm, and these effects can withstand a series of subsequent molecular changes and developmental stages, and persist [1, 4, 14].

In addition to the timing of stress occurrence, whether the stress comes from the father or the mother also influences the final genetic outcome. Stress exposure from both parents leads to completely different direct impact scenarios: if a mother experiences stress during pregnancy, the developing fetus in her womb, along with the fetus's own growing germ cells, will be directly affected by the mother's internal environment; if the father experiences stress, the stress only acts on his sperm that have not yet completed fertilization, and will not directly affect the fetus. Precisely because of this difference, to distinguish between the easily confused "intergenerational effects" and true "transgenerational inheritance", researchers must combine these two completely different exposure pathways to determine which generation is affected, and whether a true transgenerational genetic effect has occurred.

In short, the role of the developmental window is far more than just determining whether an epigenetic modification can exist on a cell; it also determines what kind of interaction this modification will have with the two rounds of epigenetic reprogramming in germ cells and embryos. What fate ultimately befalls a stress-induced epigenetic marker—whether it is completely erased by reprogramming, persists, or is re-established after being erased—depends entirely on which critical developmental window it appeared in, that is, the context of the stress exposure's occurrence [1, 4, 13].

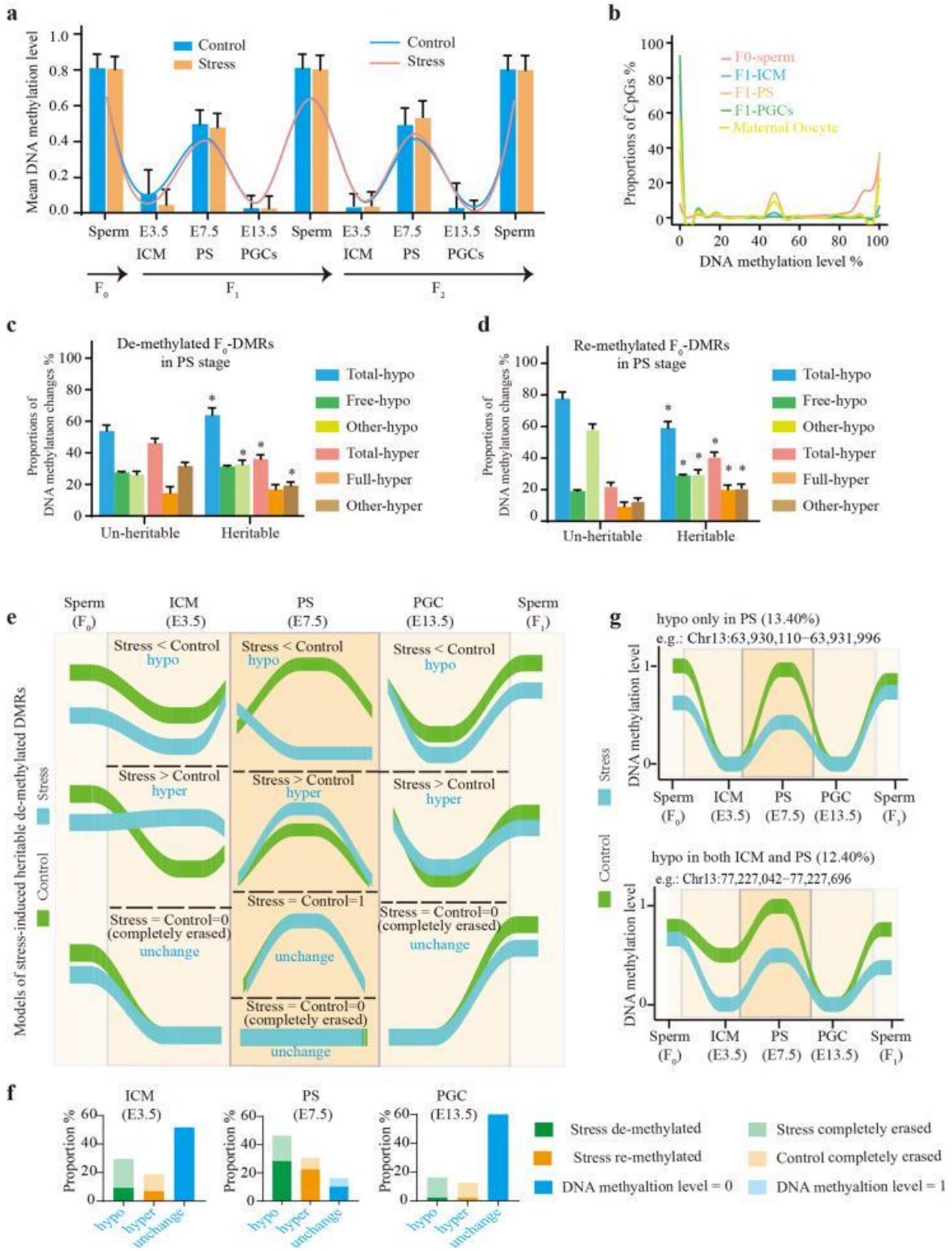


Fig. 2. Dynamic changes in stress-induced sperm DNA methylation during embryonic development [1].

C. *Molecular Regulatory Mechanisms*

In addition to the type of epigenetic modification itself and the developmental stage of the germ cell when it occurs, the body's molecular regulatory system is another core element that determines whether stress-induced epigenetic changes can be passed on. Simply put, stress leaves a set of epigenetic information in germ cells. Whether this set of information can persist throughout the entire process of embryonic development, and whether it can be re-established if it is cleared midway, is entirely determined by this molecular regulatory system. The components of this system are complex, including enzymes involved in various modification reactions, chromatin formed by the winding of DNA, and dedicated small RNA regulatory pathways in germ cells.

The core foundation of this molecular regulatory system is the working mechanism of epigenetic reprogramming. As we know, in the early stage of embryonic development, the body initiates a "reset" process that erases most of the old epigenetic markers brought in by germ cells, giving the embryo a clean starting point for development. This reset process is epigenetic reprogramming. Several key proteins operate precisely during the reprogramming process: proteins such as DNMTs are responsible for establishing DNA methylation patterns from scratch and also stably maintaining the established patterns; the TET protein that works with them is responsible for removing unnecessary methyl groups from DNA, that is, participating in the demethylation process, removing or modifying methyl groups on methyl-marked DNA. There is also another class of enzymes that modify histones; they change the compactness of chromatin, that is, alter the state of chromatin, by adding or removing specific chemical markers to histones. If the activity of the system formed by these proteins changes, the outcome of whether the stress-induced epigenetic state can be preserved during development or be completely erased will be completely different.

The selectivity of this mechanism has been confirmed by many studies, meaning it does not erase all markers indiscriminately, but processes them selectively. Those stress-related DMRs (that is, regions of DNA with methylation levels different from normal) encounter completely different fates during embryonic reprogramming. A study by Zheng *et al.* [1] found that some stress-induced DMRs are completely erased during reprogramming and disappear directly, while others reform in unique patterns. This phenomenon precisely proves that the epigenetic regulatory machinery acts selectively and does not clear all external epigenetic markers completely.

In addition to the protein-based regulatory mechanisms mentioned earlier, the small RNA pathway in germ cells is also a key gatekeeper in the entire process. One type of small RNA called piRNA plays an irreplaceable core role in maintaining the normal regulation of germ cells and protecting the stability of the genome. The main job of the piRNA pathway is to specifically control the activity of transposons in the genome—transposons are sequences that can move randomly around the genome; if they are allowed to run wild, the genome's sequence will be disrupted. piRNA keeps an eye on these sequences to ensure that the germ cell genome does not become disordered. When environmental stress acts on the body, it first changes the proportion of various RNAs in the cell. This change is transmitted all the way, interfering with gene regulation in early embryos, and ultimately leading to long-lasting trait changes [7–10].

Many solid experiments now provide reliable evidence for RNA-mediated transgenerational transmission of traits. Gapp *et al.* [7] observed that if a father experienced major trauma after birth, it would directly change the RNA pattern in his sperm. These abnormal RNAs would enter the fertilized egg during fertilization, ultimately causing offspring to also develop trauma-related traits [7]. Rodgers *et al*. [8] further confirmed that the small RNAs in sperm linked to a father's stress would interfere with the normal development of early embryos, ultimately altering the physical traits of offspring. Another study found that abnormally expressed miR-34/449 enters the pre-implantation embryo from sperm during fertilization. This finding further confirms the role of RNA in transmitting the effects of paternal stress, and illustrates that RNA is a conserved pathway for a father's environmental information to be passed to offspring.

Another easily overlooked key point is that the specific location of an epigenetic modification in the genome directly determines whether it can evade erasure by reprogramming, and whether it can be re-established even if it is reset. Not all regions of the genome follow the same rules. Some special regions, such as regions associated with repetitive sequences and imprinted regions related to parental origin effects, follow completely different regulatory rules and are not uniformly reset like other ordinary regions. Therefore, whether any epigenetic modification can ultimately be inherited by the next generation is not determined by a single factor, but by the combined effect of its type, the specific genomic location it is in, and the activity of local regulatory pathways near that location.

Overall, the body's molecular regulatory mechanisms control the outcome of every epigenetic marker: whether it is cleared by reprogramming during development, persists stably, or is re-established after being cleared. Stress first induces an epigenetic change in germ cells, but whether this change can truly be passed to the next generation depends entirely on how the body's reprogramming machinery and the various regulatory pathways of the germ cells handle this change throughout the subsequent entire development process [1, 4, 13, 15].

D. Stress Characteristics and Host Background

The nature of the stress source itself fundamentally determines what kind of epigenetic response germ cells will produce. Germ cells are the sperm and eggs responsible for reproduction, while epigenetics is a type of information that does not alter the inherent sequence of DNA but can regulate the on/off state of genes, and it changes with environmental experiences. Stress covers a very wide range, from long-term daily psychological stress, sudden traumatic events, and self-metabolic disorders to various harmful external environmental exposures. Each type activates completely different cellular response pathways in the body. For this reason, the type, intensity, duration, and timing of stress all affect the epigenetic changes within germ cells [1–4, 7].

Existing studies have confirmed that different stresses alter different regions of the sperm epigenome—the epigenome is the sum of all these epigenetic markers that regulate gene switches. For example, if a father experiences long-term psychological stress, he may develop abnormal DNA methylation in his sperm, accompanied by a series of extensive epigenetic changes, all of which could potentially affect the traits of

offspring. By contrast, trauma a father experiences after birth can disrupt the RNA regulatory mechanism in sperm and upset the normal developmental markers of offspring. This illustrates that, in the face of completely different environmental challenges, germ cells produce completely different responses.

To date, no unified theory can directly link a specific stress intensity or duration to an increased risk of transgenerational inheritance. Transgenerational inheritance refers to the impact appearing even in offspring that never directly encountered the original stress—for example, the stress a grandfather experienced still shows effects in the grandson generation, which is fundamentally different from intergenerational effects that only affect the direct next generation. What outcome ultimately occurs after encountering stress most likely depends on the combined effect of three factors: the characteristics of the stress source itself, the individual's physical and physiological response to stress, and the developmental stage of the germ cell when the stress occurs. Future research must study stress as a dynamic, multivariable process, and no longer treat it as a simple independent event.

Everyone's own basic background, including age, genetic makeup, metabolic function, and especially nutritional status, is a core factor that determines whether the epigenetic changes in germ cells can persist stably. The body's one-carbon metabolism relies on nutrients such as folate and methionine to operate; this process produces the methyl groups necessary for DNA methylation—methyl is the core material for adding switch markers to DNA, and only with it can the epigenetic regulation of germ cell genes be completed.

How a father's long-term nutritional health affects sperm quality and epigenetic regulation have now become one of the core research directions in reproductive science. Bioactive substances and micronutrients in food play key roles in regulating oxidative stress, inflammatory responses, spermatogenesis, and sperm epigenetic modifications. But whether these effects can occur is highly dependent on everyone's specific circumstances. A comprehensive systematic review and meta-analysis specifically studied the effect of supplementing methyl donor micronutrients and found that although substances such as folate, choline, betaine, B vitamins, and methionine can indeed alter DNA methylation under specific conditions, their effects vary greatly between animal experiments, in vitro experiments, and human clinical trials. This illustrates that although nutritional intervention can help maintain epigenetic stability, the outcome will vary completely due to individual and species differences.

Many human studies of real populations have also confirmed the importance of individual background characteristics. A study observed men who had experienced abuse in childhood and found unique DNA methylation markers in their sperm, as well as a profile of small non-coding RNAs linked to early life stress. This confirms that long-term environmental impacts can indeed reshape the human sperm epigenome [16]. However, many confounding variables still exist, preventing us from confirming that these epigenetic modifications can truly be passed down transgenerationally.

Differences in lifestyle can also lead to different epigenetic patterns in each person's sperm. Several recent longitudinal studies found that if fathers maintain a regular exercise habit, they can change these stress-related molecular markers and may even alter their offspring's traits during the offspring's development. This illustrates that in addition to innate genetic tendencies and daily diet, factors such as long-term healthy behaviors also tangibly affect the epigenetic state of germ cells.

The characteristics of the stress source and an individual's unique traits together determine what outcome environmental exposure will ultimately produce. Even when encountering exactly the same stress, the final epigenetic outcome will vary due to differences in each person's physiological makeup, age, metabolic status, and nutritional status. Therefore, whether an epigenetic change can stably achieve transgenerational inheritance most likely depends on two conditions at the same time: the characteristics of the stress source itself, and the biological context in which the epigenetic modification first occurred in the germ cell [4, 17, 18].

III. Preventive Interventions Against Stress-Induced Germline Epigenetic Inheritance

If the adverse changes stress causes to germ cells can be blocked in advance, the risk that environmental factors parents were exposed to will interfere with the normal development of the child in the womb can be greatly reduced. Current research in this field mainly focuses on four feasible intervention directions: adjusting daily nutritional intake, changing unhealthy lifestyle habits, conducting related treatments with antioxidants, and intervening using precise molecular technologies. However, the vast majority of existing studies have only detected sperm health quality, metabolic changes after intervention, or the physiological traits expressed in offspring; no one has directly verified that a certain intervention method can truly completely block the occurrence of transgenerational epigenetic inheritance. Moreover, there is still very little valid evidence available to confirm whether these intervention methods work in humans [2, 4, 11].

A. Nutritional and Metabolic Interventions

Nutrients ingested through daily diet affect the epigenetic regulation in germ cells through the body's one-carbon metabolism process. This process provides the necessary methyl raw materials for the methylation reaction of DNA and other molecules—that is, the core material for adding methyl markers to DNA and regulating gene switches. Key nutrients such as folate, methionine, choline, betaine, and B vitamins directly affect the availability of a core methyl donor called S-adenosylmethionine. Simply put, what parents eat and whether they take in enough nutrients directly determines

what the internal metabolic environment is like when germ cells develop [19, 20].

Experiments specifically studying the father's nutritional status also found that a man's daily dietary conditions not only affect sperm quality, but can also change the state of the epigenetic markers carried by sperm. Antioxidants and various bioactive substances in food can reduce the oxidative damage sperm receive, helping reproductive function operate normally [17]. But this does not mean that eating more nutrients that provide methyl donors will correct a disordered epigenetic state. A meta-analysis that integrated 57 studies calculated that the effect of supplementing methyl donors on DNA methylation is very unstable, with widely varying results across different studies; and human-specific clinical trials also found that compared with a placebo control group, folate supplementation did not produce consistent, clear effects across all subjects [21]. If we want to implement interventions by adjusting nutrition in the future, we cannot apply the same standardized diet plan to everyone. We must combine everyone's specific situation, adjust the dose and timing of nutritional supplements, and consider the parents' own metabolic status to formulate an appropriate plan.

B. Lifestyle and Stress-Reduction Approaches

Relieving stress for couples before they prepare to have children is a highly implementable preventive idea. Long-term exposure to psychological stress can alter the DNA methylation state in sperm, and some stress-related molecular changes have been observed in generations beyond the individual who initially experienced the stress [1]. If preconception parents are provided with psychological support, systematic stress management programs are carried out, they are helped to maintain regular exercise habits and a stable sleep schedule, the hormonal disorders, metabolic abnormalities, and inflammatory reactions that disrupt the normal development of germ cells can be reduced [18].

However, there are currently very few studies that can directly prove this set of methods is effective. Only a small number of studies have truly verified whether interventions such as exercise and psychotherapy can reverse specific stress-induced epigenetic changes and prevent these changes from being passed to offspring [2, 4, 11]. Based on the existing research conclusions, interventions that adjust lifestyle can only be defined as routine methods to reduce stress exposure and protect germ cell health, and are not yet mature schemes fully confirmed by the academic community that can completely block the transmission of epigenetic inheritance. An existing study also found that a father's maintenance of exercise can alter molecular signals in sperm, and these changes are associated with improved health levels in offspring, but the specific mechanisms of action of these signals, and their association with stress-induced transgenerational inheritance, have not yet been specifically studied [22].

C. Molecular and Epigenetic Approaches

Scientists have begun to try to find ways to directly correct those molecular changes linked to stress—these changes would otherwise be passed down through germ cells and potentially cause negative effects for offspring. The feasible directions they have currently thought of mainly include three: the first is to regulate the level of non-coding RNA, the second is to adjust specific DNA methylation patterns, and the third is to apply cutting-edge technologies such as epigenome editing. Experimental evidence has shown that some RNAs carried in sperm can be used as intervention targets. A study conducted in mice: first, male mice were exposed to long-term stress to create a model of chronic paternal stress; then, the level of miR-34c in the early embryos of these mice's offspring was restored to a normal state. In the end, all the stress-related behavioral abnormalities in these offspring actually disappeared [10].

Specifically, these stress-induced changes in small RNAs in sperm are particularly suitable intervention targets. These RNAs bound to sperm, once their levels change abnormally, will enter the early embryo along with the sperm during fertilization, interfering with the entire subsequent development process of the embryo [9]. The major premise of all such intervention schemes comes from a confirmed conclusion: specific molecular signals carried by sperm do alter the developmental trajectory of offspring [1, 4].

However, it must be remembered that all these intervention strategies are still only in the experimental stage in laboratories, and are far from being usable in humans. Performing epigenome editing on germ cells may lead to unexpected off-target effects—that is, intending to modify a specific molecular marker but accidentally changing other regions that should not be altered; in addition, this type of editing could disrupt the normal development of the embryo. More importantly, an organism's response to stress is never driven by a single mechanism, but by the coordinated work of a whole set of interrelated pathways, including DNA methylation, various RNA molecules, chromatin structure, and a series of regulatory processes during development. Therefore, adjusting only a single molecular marker may not be able to offset all the extensive biological effects caused by stress [4, 11].

IV. Challenges and Limitations

A. Limited Human Evidence and Methodological Differences

Currently, almost all the mechanistic research evidence supporting the conclusion that "stress induces epigenetic inheritance" comes from animal experiments. When conducting research on animals, researchers can proactively adjust and control the conditions for applying stress, and can continuously observe and record the trait changes of several generations of experimental animals, linking stress to subsequent genetic impacts. But applying this set of methods to humans to conduct the same strictly controllable multigenerational experiment is

completely impossible—not only are there ethical constraints, but realistic conditions also do not allow it. It is impossible to control all variables for long-term tracking as we do when manipulating animals in a laboratory, so we cannot replicate the strict research process that leads to clear conclusions as in animal experiments [2, 11].

Even when only conducting observational human studies, it is difficult to sort out the problem. There are too many confounding factors in human populations: each person's innate genetic background is different, their usual diet and daily habits are different, and their surrounding environment is also very different. All these factors jointly affect the final research results, making it impossible to separate the impact of "epigenetic changes inherited from the previous generation" from the cumulative impact of "the environment that several generations have been living in together", to clarify which factor is at play [2, 11, 12]. Beyond this, there are more confusing issues that prevent different studies from referencing and comparing with each other: the stress models used in various studies are different, the time periods when stress is applied to subjects are different, the animal strains used are different, the types of tissues collected for analysis are different, and the experimental methods used to study epigenetics are all different. Even just choosing different sequencing technologies will lead to differences in the scope and types of epigenetic modifications that can be detected in the end, further increasing the difficulty of interoperability and comparison of research results [2, 5, 11].

B. Difficulty Establishing Causation and Stable Transmission

Many studies have recorded that after a person encounters stress; epigenetic-level differences appear in their body. But there is an unavoidable logical trap here: even if you observe two phenomena at the same time—DNA methylation in sperm or eggs has changed, and some special physiological or behavioral trait is also found in that person's offspring, you cannot directly conclude that this epigenetic change caused that trait in the offspring. The only way to obtain solid evidence that can confirm causation is to conduct experiments that stringently connect the entire chain of influence from start to finish: first confirm that the individual was indeed exposed to stress, then track the specific molecular changes that occurred in their germ cells, follow up on whether there are any abnormalities throughout the entire embryonic development process, and finally, long-term track the health and development status of offspring. Only when every causal link is aligned can the conclusion be considered valid [1, 11].

In addition to the difficulty of proving causation, the physiological process of epigenetic reprogramming itself is another core obstacle standing in the way of research. For mammals, regardless of whether it is a newly formed early embryo or a germ cell still in the development process, it will undergo large-scale epigenetic remodeling throughout its maturation. This process is equivalent to performing a "system reset" on the new cell; the vast majority of the original DNA methylation markers and regulatory markers on chromatin are either completely erased or re-established according to developmental needs, to ensure the normal growth of embryos and germ cells. When placed in the scenario of stress-induced epigenetic changes, this creates a difficult problem to solve: even if you clearly observe stress-related molecular changes in mature sperm, these changes may be completely erased in the reprogramming reset process before they can affect subsequent embryonic development. To this day, researchers have not understood the underlying rule—why some molecular signals can evade erasure and persist, while others are completely erased [1, 4].

C. Intergenerational Versus Transgenerational Effects

Researchers conducting this type of research must first clarify two core concepts: one is intergenerational effects, and the other is true transgenerational epigenetic inheritance. In some experimental models used to simulate stress exposure, the initial stress source applied not only affects the parent generation that personally endured the stress, but also spreads to the offspring that were developing in the parent's body at the time, and even the germ cells carried by these offspring themselves will be affected. This leads to a situation where if special traits are only observed in the next generation, it cannot be directly assumed that this is transgenerational inheritance—the traits of this generation likely appeared because they were directly exposed to the stress source, not because they inherited any epigenetic information from the parent generation [4, 11, 13].

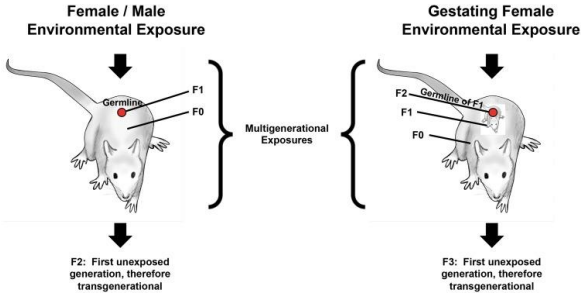


Fig. 3. Intergenerational vs transgenerational inheritance.

V. Future Perspectives

A. Identifying Heritable Molecular Changes

The first thing future research must do is distinguish between the temporary physiological responses caused by stress and those molecular changes that can withstand epigenetic reprogramming and truly affect offspring. Simply put, we must first clarify which are short-term reactions that temporarily emerge after the body encounters stress, and which are stable changes that survive the epigenetic reset during development and can persist into the next generation. Only the latter can truly affect offspring. Next, multigenerational follow-up studies with more unified standards need to be designed to clarify the unique role of epigenetic mechanisms in heritable traits [1, 4, 15].

For environmental information to achieve intergenerational transmission, that is, to pass the environmental impact of the previous generation to the next, it may rely on the coordinated work of DNA methylation, non-coding RNA, chromatin organization, and gene expression. These types of mechanisms must work together to transmit environmental signals intact. Combining technologies such as single-cell research and multi-omics methods will help accurately locate those specific molecular changes that persist in all developmental stages, and not miss any key signal that can be retained across developmental stages.

B. *Establishing Causal Mechanisms and Critical Developmental Windows*

Future research must focus its efforts in two directions, to first solve the two most core problems. The first direction is to figure out which developmental stage of germ cells is most sensitive to stress, and also identify those molecular changes that truly affect offspring development—they are not irrelevant changes that only coincidentally appear with stress, but molecular changes that truly have direct impacts on a child's growth. We can gather and compare the scattered studies related to each stage of germ cell development, including studies on the development process of primordial germ cells, the maturation process of sperm, the maturation process of eggs, and related studies on the preconception period for couples. Cross-analyzing these studies together may help identify those critical developmental windows—that is, when a person is exposed to harmful environmental factors during this stage, these effects will persist and bring long-term changes to offspring [4].

There is also a second direction: we can also verify the role of molecular changes through precise experimental operations. Specifically, by artificially adjusting those candidate DNA methylation sites, or the RNAs in sperm linked to the effects of stress, this active experimental intervention will allow us to figure out a core question: does this molecular change truly cause a trait that can be passed to the next generation, or does it only coincidentally appear when stress is encountered and has no causal relationship with the inherited trait [4, 9, 11].

C. *Developing Preconception and Public Health Strategies*

The preconception window, when couples are planning to have children, may be an excellent opportunity for intervention—we can act during this stage to reduce the various negative impacts of stress on germ cells. Future research must clarify several questions: if we help prospective parents reduce psychological stress, regulate their body's metabolic status, and provide them with appropriate nutritional support, can we bring the already abnormal germ cell epigenetic profile back to a normal state, and ultimately reduce the risk of various health problems after the child is born [17, 20].

Looking at a longer timeline, the accumulated results of these studies can also be used to design a formal preconception health service program, which incorporates regular stress screening and assessment, supporting psychological services, personalized nutritional guidance, and full-cycle reproductive health monitoring, to provide comprehensive support for preconception families. However, one point must be clarified: currently, we must never treat the various discovered epigenetic markers as absolute evidence that a person will definitely develop a certain disease in the future. The exact associations between these markers and long-term health outcomes have not yet been fully studied, so they cannot be used to draw definitive conclusions [2, 11].

VI. Conclusion

Stress can induce epigenetic changes in germ cells, which is another clear example of how environmental factors can affect the state of offspring without modifying the inherent sequence of DNA, only by regulating the activation or silencing of genes. But the presence of these epigenetic changes in germ cells does not equate to the occurrence of transgenerational inheritance—not all changes that appear in germ cells can be stably passed down from generation to generation. To clarify these two issues, two concepts must first be completely separated: one is intergenerational effects, that is, the impact of stress directly acting on the individual who experienced it, and the next generation that developed bound to that individual; the other is true transgenerational inheritance, that is, offspring who never directly encountered the original stress are also affected. Defining the boundary between the two is a crucial prerequisite for all research in this field.

All the data analyzed in this paper show that whether stress-induced germline epigenetic changes can be passed to offspring is never determined by a single factor, but is the result of a series of variables working together. These variables include the nature and stability of the epigenetic change itself, that is, what type of epigenetic modification it is and how stable it is; which developmental stage the germ cell is in when the stress occurs; how the molecular mechanisms that regulate epigenetic reset work; as well as the characteristics of the stress source itself, and the characteristics of the organism carrying the stress. Simply put, even if stress-induced epigenetic changes are indeed detected in sperm, it does not mean they will definitely be passed to the next generation. Whether they can ultimately be inherited depends largely on whether they can evade erasure by natural epigenetic reprogramming during the development of germ cells and embryos—the large cleaning process the body performs to reset epigenetic markers in developing cells; even if they are temporarily erased, it depends on whether they can be re-established later. If they cannot pass these two checkpoints, this change cannot be passed to the next generation.

The findings organized in this paper lay the foundation for us to develop strategies to prevent harmful transgenerational epigenetic effects. Currently, potential directions to try include nutritional interventions, drug treatments, lifestyle adjustments, and molecular methods that can target abnormal epigenetic markers. But almost

all the scientific evidence supporting these directions currently comes from animal experiments. If these strategies are used in humans, whether they can truly prevent transgenerational inheritance in humans, and what safety risks they may carry, there is a serious lack of relevant safety data. Future research must prioritize clarifying two things: which stress-related epigenetic changes truly can be transmitted between generations, and what specific conditions must be met for this transmission to occur.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Yuchen Zhou and Yike Guo conceived the overall structure of this review and performed literature search and screening. Yuchen Zhou summarized evidence for epigenetic modification mechanisms and drafted the abstract, introduction, and Sections II.A–II.C. Yike Guo organized content regarding germ-cell developmental windows, stress-host interactions, preventive interventions, research challenges, and future perspectives, and wrote Sections II.D–V. Both authors revised the full-text manuscript, checked citations and reference formatting, and edited figure captions. All authors have read and approved the final version of the manuscript.

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Yuchen Zhou and Yike Guo contributed equally to this work and should be considered co-first authors.

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