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# Epigenetics and a new era of biological weapons

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**Highlights**
- The research of epigenetic inheritance mechanisms opens up possibilities for creating new types of biological damaging agents and changing the targets and methods of biological warfare.
- The use of epigenetic mechanisms for *in vivo* gene expression manipulation requires the development of strict international regulatory protocols, biosecurity systems, and broad public discussion about the ethical boundaries of scientific intervention.

***Relevance.*** Driven by the explosive interest of molecular biologists in studying small RNAs and the epigenetic changes they cause in the inheritance of phenotypic traits.

***The purpose of the study*** is to identify the level and directions of research on small RNAs capable of inducing pathological processes.

***The source base of the study***. Articles from scientific journals accessible through the PubMed search engine.

***Research method.*** Analytical.

***Results.*** The current level of understanding of epigenetic gene control mechanisms allows for targeted in vivo gene expression management and impact on future generations through epigenetic modifications. Hundreds of pathological conditions caused by interference with the epigenetic regulation of phenotypic traits have been identified. Technologies have been developed for the artificial introduction of specific small RNAs (sRNAs) into germ cells that are not "products" of maternal/paternal "genetic material." These sRNAs accumulate in germ cells (oocytes, spermatozoa) and are transmitted to offspring after fertilization, i.e., to the next generation(s). sRNAs are known for their long-term stability and resistance to RNases. They can enter the human body through food, aerosol routes, parenterally (vaccines, DNA/RNA preparations) and be transmitted to subsequent generations.

***Conclusions***. The development of epigenetic gene control technologies carries unprecedented risks. Uncontrolled or malicious application of these tools could lead to catastrophic consequences, including:
- A sharp increase in pathologies in subsequent generations due to off-target effects that can be inherited;
- Disruption of the genetic stability of the human population due to unpredictable long-term consequences of interference with the epigenome;
- Targeted depopulation of specific ethnic groups or whole humankind.

***Keywords:*** *biological weapons; biosecurity; epigenetic inheritance; epigenetic weapons; epigenetics; expression manipulation; genetic stability; heritable pathologies; heritable pathologies; population destabilization; small RNAs, sRNAs; targeted gene; transgenerational inheritance*

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# Эпигенетика и новая эра биологического оружия

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**Основные моменты**
- изучение механизмов эпигенетического наследования открывает возможности создания биологических поражающих агентов нового типа и, соответственно, изменения целей и способов ведения биологической войны;
- использование эпигенетических механизмов для манипуляции экспрессией генов *in vivo* требует разработки строгих международных протоколов регулирования, систем биобезопасности и широкой общественной дискуссии о этических границах научного вмешательства.

***Актуальность***. Обусловлена взрывным интересом молекулярных биологов к изучению малых РНК и вызываемых ими эпигенетический изменений в наследовании фенотипических признаков.
***Цель исследования*** – выявить уровень и направления исследований малых РНК, способных вызывать патологические процессы.
***Источниковая база исследования.*** Статьи из научных журналов, доступные через поисковую систему PubMed.
***Метод исследования.*** Аналитический.
***Результаты.*** В настоящее время уровень изученности эпигенетических механизмов управления генами позволяет целенаправленное управление экспрессией генов *in vivo* и воздействие на будущие поколения через эпигенетические модификации. Установлены сотни патологических состояний, вызванные вмешательством в эпигенетическую регуляцию фенотипических признаков. Разработаны технологии искусственного введения в половые клетки определенных малых РНК (sRNA), не являющихся «продуктом» материнского/отцовского «генетического материала». Эти sRNA накапливаются в половых клетках (ооцитах, сперматозоидах) и после оплодотворения передаются потомству, т.е. следующему поколению (поколениям). sRNA известны своей долговременной стабильностью и устойчивостью к РНКазам. Они могут проникать в организм человека с пищей, аэрозольным путем, парентерально (вакцины, препараты ДНК и РНК) и передаваться в следующие поколения.
***Заключение.*** Развитие технологий эпигенетического управления генами несет в себе беспрецедентные риски. Неконтролируемое или злонамеренное применение этих инструментов способно привести к катастрофическим последствиям, включая резкий рост патологий у последующих поколений вследствие нецелевых эффектов, которые могут наследоваться; нарушения генетической стабильности человеческой популяции из-за непредсказуемых долгосрочных последствий вмешательства в эпигеном, а также целенаправленную депопуляции отдельных этнических групп или человечества в целом.

***Ключевые слова:*** *биобезопасность; биологическое оружие; внутрипоколенческое наследование; генетическая стабильность; дестабилизация популяции; малые РНК; направленное изменение экспрессии генов; наследственные патологии; эпигенетика; эпигенетическое оружие; эпигенетическое наследование*

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According to Darwin's Pangenesis, cells could "throw off" minute gemmules, which were capable of diffusion from cell to cell or circulation through the body, modification by changes of the environment and the effects of use and disuse, union with germ cells, and transmission from parent to offspring. If the cells of the body are modified by changes in the environment or by the effects of use and disuse, they would shed modified gemmules, which are transmitted with their acquired characters to the offspring [1]. Today Darwin's gemmules are described as "extracellular vesicles". Extracellular vesicles (EV) are a heterogeneous group of cell-derived membranous structures comprising exosomes (size 50–150 nm) and microvesicles (50–500 nm (up to 1 μm)) [2]. Study of extracellular vesicle composition revealed that they can carry various cargoes, including proteins, lipids and nucleic acids, and this content can vary widely between cells and conditions. Apart from proteins, extracellular vesicles also carry nucleic acids, including RNAs (mRNAs and non-coding RNAs, including small RNAs (sRNAs)) and DNA sequences. sRNAs have been shown to be differentially sorted to exosomes depending on their sequence (presence of specific motifs), which indicates that incorporation of nucleic acids into exosomes is regulated. It has been shown that exosome-mediated transfer of mRNAs and small RNAs (sRNAs) is a novel mechanism of genetic exchange between cells [2].

The literature about EV is extensive, new and newer comprehensive descriptions are appearing [3–6]. It should be noted that mainly the EV with small RNAs cargo which modify recipient cell protein production and gene expression (here in the germ cell lines) today "update" Darwin's more than 150 years old genial idea of the inheritance of acquired characters ("pangenesis") [1, 7, 8].

However, there are two sites of the same coin. From history, we know that the research of uranium fission in the early 20 century led on one hand to nuclear powerhouses, on the other hand to the creation of nuclear weapons. Research into the inheritance of "acquired characteristics" is a path toward changing human heredity. The hereditary "changes" can cure or significantly improve hereditary diseases. On the other hand, it can lead to incredible increase of pathological casualties, human sterility and even to depopulation of "selected" ethnic groups, or the whole humankind. These changes would be irreversible, and they would be recognized rather late.

This study has been evoked by the explosive interest of molecular biologists in studying small RNAs and the epigenetic changes they cause in inheritance.

*The purpose of the study.* To identify the level and directions of research on small RNAs capable of inducing pathological processes.

*The source base of the study.* Articles from scientific journals available through the PubMed search engine.

*Research method.* Analytical.

Tasks Addressed:

- a theoretical introduction to the extensive world of small RNAs;
- examination of the mechanisms of epigenetic inheritance;
- the potential for dual-use of the technology.

**Small RNAs (sRNA).** According to "Selection on the epigenome: small RNA inheritance in animal evolution", the epigenetic alterations include DNA methylation, histone modifications, and the production of sRNAs [9]. Recent work across the tree of life has shown that environmentally induced epigenetic modifications can be stably inherited by offspring which were never exposed to the original environment, a process termed transgenerational epigenetic inheritance (TEI). TEI can be beneficial in stressful environments, for example under starvation or in the presence of pathogens. Nevertheless, some authors have found non-adaptive or maladaptive TEI effects ncRNAs (non-coding RNAs) are RNA molecules that are transcribed from DNA but do not encode proteins [10, 11]. They can be further divided into several categories based on their function and size[1]. For example:

i) Small ncRNAs: These include microRNAs (miRNAs), small interfering RNAs (siRNAs), and PIWI-interacting RNAs (piRNAs). These ncRNAs are typically 20–25 nucleotides in length and function by regulating gene expression.

ii) Long ncRNAs: These are ncRNAs that are more than 200 nucleotides in length and often play structural roles in the cell. Examples

[1] Non-Coding RNAs (ncRNAs). URL: https://alcartez.github.io/Bioinformatics_Guides/ncRNA_Guide/ (date: 13.05.2025).

include Xist, which plays a role in X-chromosome inactivation, and HOTAIR, which plays a role in chromatin remodeling.

iii) Other ncRNAs: There are many other types of ncRNAs, including tRNA-derived small RNAs (tsRNAs), repeat-associated small interfering RNAs (rasiRNAs), and natural antisense transcripts (NATs), among others. These ncRNAs may have a variety of functions, including regulation of gene expression, RNA processing, and DNA modification.

There are many different types of ncRNAs, and they can be classified based on their size, structure, and function. Some common types of ncRNAs include:

i) microRNAs (miRNAs): These are small ncRNAs (typically 20–25 nucleotides in length) that regulate gene expression by binding to the 3' untranslated region (3' UTR) of target mRNAs and inhibiting their translation.

ii) small interfering RNAs (siRNAs): These are also small ncRNAs (typically 20–25 nucleotides in length) that play a role in the RNA interference (RNAi) pathway, which is a process that silences specific genes.

iii) PIWI-interacting RNAs (piRNAs): These are small ncRNAs (typically 23–30 nucleotides in length) that are involved in the regulation of transposons (mobile genetic elements) and the repression of transposon-derived small RNAs.

iv) Xist: This is a long ncRNA (typically 17 kilobases in length) that plays a role in X-chromosome inactivation, a process that ensures that females have the same amount of X-chromosome gene expression as males.

v) HOTAIR: This is a long ncRNA (typically 2.2 kilobases in length) that plays a role in chromatin remodeling, which is the process of modifying the structure of chromatin (the complex of DNA and proteins that make up the chromosome).

vi) tRNA-derived small RNAs (tsRNAs): These are small ncRNAs (typically 18–30 nucleotides in length) that are derived from tRNAs (transfer RNAs) and play a role in the regulation of gene expression.

vii) repeat-associated small interfering RNAs (rasiRNAs): These are small ncRNAs (typically 21–24 nucleotides in length) that are involved in the regulation of transposons and the repression of transposon-derived small RNAs.

viii) natural antisense transcripts (NATs): These are ncRNAs that are transcribed from the opposite strand of DNA as the sense strand and may play a role in the regulation of gene expression.

The small – sRNAs were extensively reviewed, and we will explain only additionally necessary facts when required [12].

The sRNA inheritance system consists of all sRNA transcripts, precursors, interacting proteins, and other cellular components that interact to regulate or silence gene activity and elicit inheritance independently of the causative stressor. In this context, it is irrelevant which specific silencing mechanism (e.g., degradation of complementary transcripts and/or histone modifications) is involved—the sole criterion is that these changes are initiated through the production of sRNAs and are inherited by the next generation.

sRNAs are traditionally divided into three groups—small interfering RNAs (siRNAs), PIWI-interacting RNAs (piRNAs), and microRNAs (miRNAs). sRNAs interact with argonaute (AGO) proteins to form an RNA-induced silencing complex (RISC) that elicits gene expression changes via complementary base-pairing. Many AGO proteins directly cleave targets via endonucleases. However, some AGO proteins recruit additional components to RISC, such as methyltransferases which deposit methylation (*Figure 1*).

To show how complex the situation looks like, we mention a picture of the biogenesis of small RNAs and long ncRNAs (lncRNAs) (*Figure 2*).

The small and long non-coding RNAs are not "detached".They are in a state of "cross-interaction," which enables them to disrupt the functioning of gene networks, i.e., hundreds of genes simultaneously (*Figure 3*).

As mentioned above, to the group of small RNAs belong the tRNAs and tRNA-derived small RNAs (tsRNAs). The immense complexity of post-transcriptional modifications, shown in *Figure 4*, suggests catastrophic consequences for human health from any external intervention.

The roles of the tRNA modifications and their connections to human diseases are shown in *Figure 5*.

The tRNA derived RNAs (tDRs), also known as tRNA fragments (tRFs) and tRNA-derived small RNAs (tsRNAs), are cleavage products from tRNA precursors and mature tRNAs. To date, more than 20,000 different tDRs have been discovered, which differ in length and sequence [16].

These tDRs have emerged as essential regulators of many biological processes, such as transposon activation, translation, innate immune responses, transgenerational inheritance, and development [17, 18].

However, the rapid expansion of this field has led to confusion in their nomenclature. Therefore, a tDR name system, an algorithm designed to standardize the naming of tDRs has been developed [19].

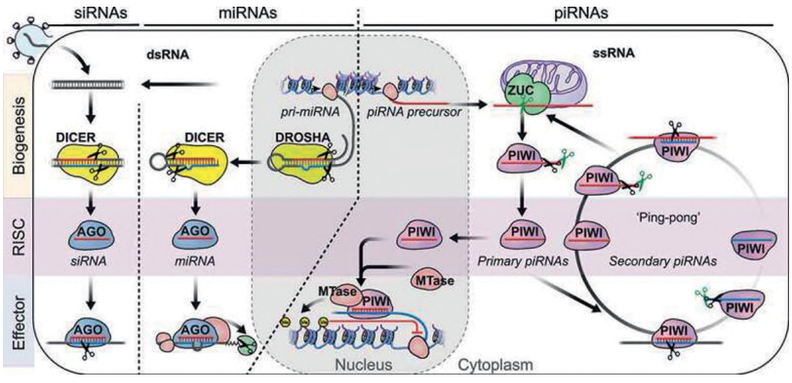


**Figure 1:** *A simplified schematic illustrating the three primary pathways of small RNA biogenesis in animals and their role in regulating or suppressing gene activity. Small interfering RNAs (siRNAs) originate from long double stranded RNA (dsRNA) and are generated by the RNase III enzyme Dicer. SiRNAs associate with AGO-clade Argonaute proteins and degrade target RNA using the slicer activity of Argonaute proteins. MicroRNAs (miRNAs) originate from partly double-stranded RNA hairpins. MiRNA biogenesis proceeds in two steps involving the RNase III enzymes DROSHA and DICER. MiRNAs associate with AGO-clade Argonaute proteins and recruit RNA-degradation machinery to silence their targets post-transcriptionally (PTGS). PIWI-interacting RNAs (piRNAs) originate from long single-stranded precursors. Their biogenesis involves the endonuclease Zucchini/PLD6(ZUC) (primary piRNAs), or piRNA-guided slicing during ping-pong (secondary piRNAs). Maturation of some piRNAs involves additional 3' trimming. PIWI-piRNA complexes degrade target-RNA in the cytoplasm or establish lasting epigenetic restriction in the nucleus. The whole Figure and the text were taken from [13]*

**Рисунок 1** – *Упрощенное схематическое изображение трех основных путей биогенеза малых РНК у животных, влияющих на регуляцию или подавление генной активности. Малые интерферирующие РНК (миРНК, siRNAs) образуются из длинных двуцепочечных РНК (дцРНК) при участии РНКазы III Dicer. миРНК связываются с белками Argonaute (AGO) и расщепляют молекулы РНК-мишени благодаря эндонуклеазной активности («slicer») этих белков. МикроРНК (миРНК, miRNAs) образуются из частично двуцепочечных шпилечных структур РНК. Их биогенез осуществляется в два этапа с участием РНКаз III DROSHA (в ядре) и DICER (в цитоплазме). миРНК связываются с белками Argonaute (AGO) и направляют аппарат деградации РНК для посттранскрипционного сайленсинга генов-мишеней (ПТГС, PTGS). PIWI-взаимодействующие РНК (пиРНК, piRNAs) образуются из длинных одноцепочечных предшественников. В их биогенезе участвует эндонуклеаза Zucchini/PLD6 (ZUC) (первичные пиРНК) или механизм «пинг-понг» с участием самих пиРНК (вторичные пиРНК). Созревание некоторых пиРНК включает дополнительное укорочение с 3'-конца. Комплексы PIWI-piRNA расщепляют РНК-мишени в цитоплазме или устанавливают долгосрочное эпигенетическое репрессия транскрипции в ядре. Рисунок и текст заимствованы из [13]*

Circular RNAs (circRNAs) are a large family of non-coding RNAs characterized by a single-stranded, covalently closed structure, predominantly synthesized through a back-splicing mechanism. While thousands of circRNAs have been identified, only a few have been functionally characterized. Although circRNAs are less abundant than other RNA types, they exhibit exceptional stability due to their covalently closed structure and demonstrate high cell and tissue specificity. CircRNAs play a critical role in maintaining cellular homeostasis by influencing gene transcription, translation, and post-translation processes, modulating the immune system, and interacting with mRNA, miRNA, and proteins. Abnormal circRNA expression has been associated with a wide range of human diseases and various infections [20–22].

CircRNAs are translated under conditions that favor cap-independent translation, notably in cancer and generate proteins that are shorter than mRNA-encoded proteins, which can acquire new functions relevant to diseases [22]. The situation is rather complex and to "unpredictable". As suggested by Zhang and Zhao [23], the employment of the AI or "deep learning technologies" for analyzing these complex data became mandatory.

So far, we have shown comprehensive, theoretical "introduction" into the big world of sRNA (small RNAs). However, all diseases presented above (e.g. in *Figure 5* for "tRNA modifications and connections to human diseases") are those which today are known as "heritable". This means that they are inherited as somatic mutations of the human genome. The novel kind of possible biological weapons would not rely on these mechanisms. We have in mind the "environmentally" induced sRNA inheritance. In other words, an artificial introduction (application) of certain sRNAs

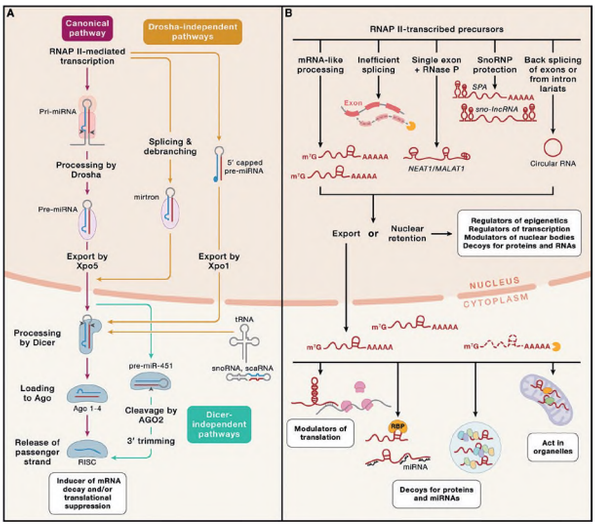


**Figure 1:** *Biogenesis of small RNAs and lncRNAs. A, Well-defined biogenesis pathway of miRNAs. B, Diverse biogenesis pathway and features of lncRNAs. The whole Figure and the text were taken from [14]*

**Рисунок 1** – *Биогенез малых РНК и длинных некодирующих РНК (длнкРНК). А – Детально охарактеризованный путь биогенеза микроРНК (миРНК). В – Разнообразие путей биогенеза и функций длинных нкРНК (длнкРНК). Рисунок и текст заимствованы из [14]*

which are not a "product" of the maternal/paternal "genetic material". These sRNA would accumulate in the germ cells (oocytes, sperm) and after fertilization would be transmitted to the offspring – i.e. next generation(s). sRNAs are known for their long-time stability and resistance to the RNAses. They can be transmitted to the organism by food, aerosol, parenterally (vaccines, DNA and RNA preparates). As will be shown below the substitution of uridine with pseudouridine and its methylation to N1-methylpseudouridine further enhances the RNA stability and can guide transport of sRNA to the germline. The consequences could be disastrous. Not to be recognized immediately the effect(s) could be irreversible. Different diseases of the F0 (parental) and further F1, F2, …, FX generations and depopulations (among others) of different ethnic groups.

Environmentally induced sRNA inheritance has been documented in model species such as *Caenorhabditis elegans* [24], *Drosophila melanogaster* [25], and mice [26].

One of the most exciting observations of epigenetic inheritance has been described in 2014 by Dias and Ressler [27]. The authors subjected F0 mice to odor fear conditioning before conception and found that subsequently conceived F1 and F2 generations had an increased behavioral sensitivity to the F0-conditioned odor, but not to other odors. When an odor (acetophenone) that activates a known odorant receptor (Olfr151) was used to condition F0 mice, the behavioral sensitivity of the F1 and F2 generations to acetophenone was complemented by an enhanced neuroanatomical representation of the Olfr151 pathway. Bisulfite sequencing of sperm DNA from conditioned F0 males and F1 naive offspring revealed CpG hypomethylation in the Olfr151 gene. In addition, *in vitro* fertilization, F2 inheritance and cross-fostering revealed that these transgenerational effects are inherited via parental gametes. The authors state: "In summary, we have begun to explore an under-appreciated influence on adult behavior—ancestral experience before conception. From a translational perspective, our results allow us to appreciate how the experiences of a parent, before even conceiving offspring, markedly influence both structure and function in the nervous system of subsequent generations. Such a phenomenon may contribute to the etiology and potential intergenerational transmission of risk for neuropsychiatric disorders, such as phobias, anxiety and posttraumatic stress disorder. To conclude, we interpret these results as highlighting how generations can inherit information about the salience of specific stimuli in ancestral environments so that their behavior and neuroanatomy are altered to allow for appropriate stimulus-specific responses." In summary, when mice were trained with acetophenone, the F1 and F2 generations showed a heightened startle response in the presence of acetophenone, but not in the presence of propanol. When the ancestors were instead trained with propanol, their descendants were fearful in the presence of propanol, but not acetophenone. The authors showed that the response was transmitted through either the male or female germ line up to two generations, suggesting that both sperm and egg DNA register the exposure as an epigenetic mark.

In the comment [28] – "the authors propose that germ cells, which are known to contain olfactory receptors, are activated by odor and trigger a signaling pathway that targets site-specific DNA methylation. However, this is not sufficient to explain how these changes in DNA methylation in olfactory receptors are linked to the fearful experience. Thus, there must be sensors of behavioral experience in the gamete that are as yet unknown and that could incorporate the brain signals into several addresses in the sperm genome (*Figure 6*). Sperm olfactory receptors could be a component of such machinery, as well as hormone receptors such as glucocorticoid receptors. Other attractive candidates include sRNAs, which could potentially circulate

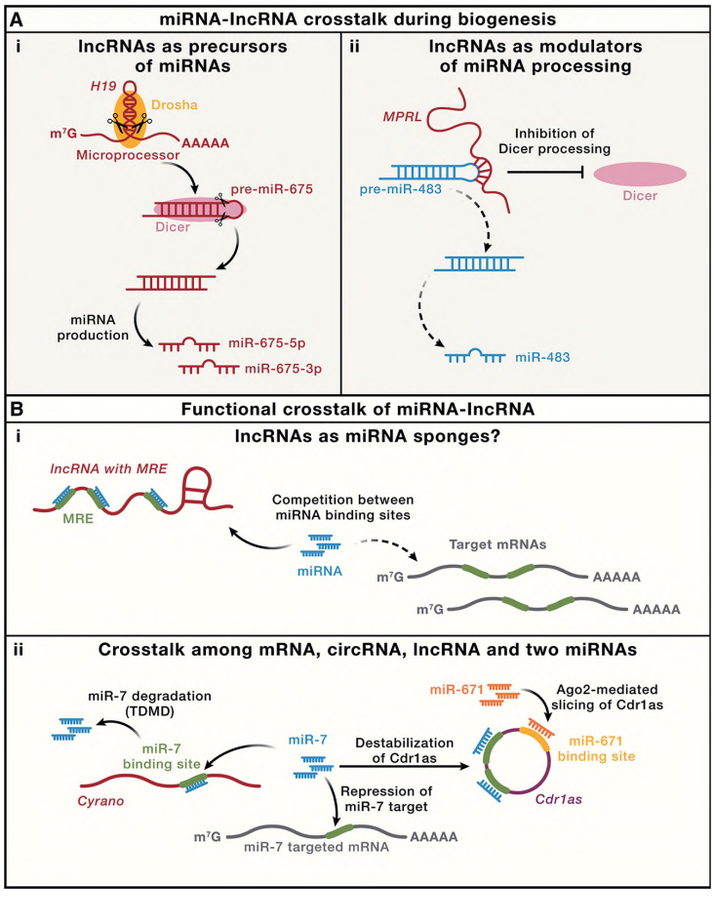


**Figure 3:** *Crosstalk between small RNAs and lncRNAs. A, The crosstalk between miRNA and lncRNA during biogenesis. (Left) Some lncRNAs contain local hairpin structures that yield miRNAs, serving as pri-miRNAs, illustrated by the H19 lncRNA whose hairpin produces two conserved miRNAs, miR-675-3p and miR-675-5p. (Right) Long non-coding RNAs can block miRNA maturation. As an example, the lncRNA MPRL pairs with the apical loop region of pre-miR-483, interfering with its interaction with DICER, resulting in a decrease of miR-483 production during cisplatin-induced stress. B, Functional crosstalk between miRNAs and lncRNAs. (Left) Some abundant lncRNAs may regulate (enhance or block) gene expression by decoying miRNAs. Of note, this miRNA sponge (ceRNA) hypothesis is unlikely to occur in physiological conditions unless the sponge RNA is highly abundant and contains multiple high-affinity, closely spaced miRNA binding sites (MREs). Thus, the stoichiometric ratio of examined RNAs should be critically evalu ated. (Right) Complex crosstalk among miRNAs, the lncRNA Cyrano, and the circular RNA Cdr1as. Cyrano base pairs with miR-7 trigger miR-7 degradation via target-directed microRNA degradation (TDMD), protecting Cdr1as from miR 7-mediated destruction in neurons. Another miRNA, miR-671, binds to Cdr1as and induces Ago2-catalyzed slicing of Cdr1as. The whole Figure and the text were taken from [14]*

**Рисунок 3** – *Взаимодействие (кросс-ток) между малыми и длинными нкРНК. А – Взаимодействие в процессе биогенеза. Слева – некоторые длинные некодирующие РНК содержат шпилечные структуры, служащие предшественниками для миРНК (pri-miRNAs). Например, шпилька в транскрипте длинной некодирующей РНК H19 генерирует консервативные миР-675-3р и миР-675-5р. Справа – длинные некодирующие РНК могут блокировать созревание миРНК. Длинная некодирующая РНК MPRL связывается с апикальной петлей pre-миР-483, блокируя его взаимодействие с DICER и снижая продукцию зрелого миР-483 в условиях стресса, индуцированного цисплатином. В – Функциональное взаимодействие. Слева – избыточные длинные некодирующие РНК могут регулировать (усиливать или блокировать) экспрессию генов, выступая в роли «приманки» (decoy) для миРНК (гипотеза «миРНК-губки»; или ceRNA – competitive endogenous RNA, конкурирующая эндогенная РНК). Для реализации этого механизма в физиологических условиях требуется высокая концентрация РНК-приманки с множественными высокоаффинными сайтами связывания миРНК (MRE), что делает необходимым критическую оценку стехиометрического соотношения РНК. Справа – сложное взаимодействие между миР-7, длинной некодирующей РНК Cyrano и кольцевой РНК Cdr1as. Cyrano комплементарно связывается с миР-7, запуская ее деградацию по механизму TDMD (деградация микроРНК, направляемая мишенью), и защищает Cdr1as от разрушения. Одновременно миР-671 связывается с Cdr1as и индуцирует его расщепление при катализе Ago2. Рисунок и текст заимствованы из [14]*

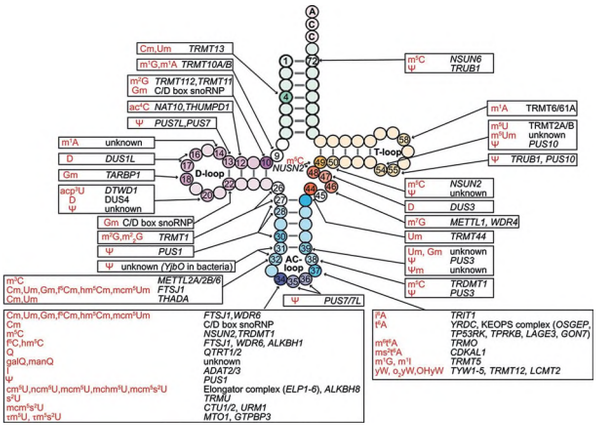


**Figure 4:** *Schematic representation of human cytoplasmic tRNA modifications and their writer enzymes. Modified nucleotides are numbered. Each type of tRNA modification and their modifying enzymes are indicated. Modification enzymes that are confirmed in other organisms are listed in parentheses. The abbreviation of each RNA modification conforms with the RNA modification database MODOMICS. The whole Figure and the text were taken from [15]*

**Рисунок 4** – *Схематическое изображение модификаций цитоплазматической мРНК человека и ферментов, их осуществляющих. Модифицированные нуклеотиды пронумерованы. Указаны тип модификации и соответствующие ферменты. Ферменты, подтвержденные у других организмов, указаны в скобках. Сокращения модификаций соответствуют базе данных MODOMICS. Рисунок и текст заимствованы из [15]*

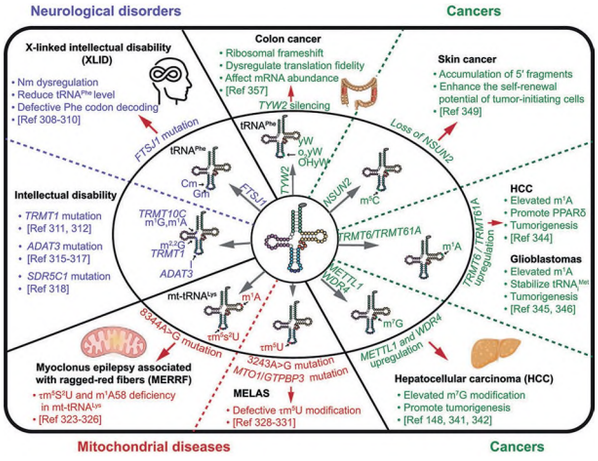


**Figure 5:** *tRNA modifications and connections to human diseases. Schematic representation of the relationship between abnormal tRNA modifications and various human diseases, with a focus on neurological disorders, mitochondrial disorders, and cancers. The whole Figure and the text were taken from [15]*

**Рисунок 5** – *Модификации мРНК и их связь с заболеваниями человека. Схематическое представление взаимосвязи между нарушениями модификаций мРНК и различными заболеваниями человека, с акцентом на неврологические расстройства, митохондриальные патологии и онкологические заболевания. Рисунок и текст заимствованы из [15]*

systemically from brain to sperm and target specific sequences in the genome. The changes in DNA methylation must be protected in the germ line and transmitted during cellular differentiation to guide the formation of circuitry and anatomical densities of olfactory receptors during brain development. The lack of differential methylation in the mature olfactory receptor neuron might indicate that these differentially methylated gene targets are critical for the developmental stages and disappear once the relevant circuitry is established."

This study by Dias and Ressler [27] provides strong evidence that the germline can serve as a vector for transmitting lessons from adult experience across generations. Future studies are needed to determine how important these mechanisms are in humans and whether they influence the rapid evolution of phenotypes seen in human populations."

In humans exposed to violence epigenetic "signatures" have been observed in three generations [29]. Here, the authors discuss the possibility that maternal trauma influences infant and adult health outcomes and may impact future generations through epigenetic modifications such as DNA methylation (DNAm). The authors assessed DNAm signatures of war-related violence by comparing germline, prenatal, and direct exposures to violence across three generations of Syrian refugees. They compared families in which a pregnant grandmother versus a pregnant mother was exposed to violence and included a control group with no exposure to war. They collected buccal swab samples and survey data from mothers and 1–2 children in each of 48 families (n=131 participants). Based on an epigenome-wide association study (EWAS), the authors were able to identify differentially methylated regions (DMPs): 14 DMPs were associated with germline and 21 DMPs were associated with direct exposure to violence. The largest difference in DNAm relative to unexposed controls was observed at a germline-associated DMP, cg01490163, with lower DNAm among those exposed in germline (Difference: –0.265, 95% confidence interval (CI) – 0.349, –0.181). The site is approximately 3 kb upstream of Keratin 36 (KRT36), which produces keratin and has a potential role in some cancers. Compared to controls, the highest DNAm was observed at the germline-associated DMP, cg07462448, and two direct-associated DMPs, cg14117527 and cg14832449. Site cg07462448 is annotated to Caspase 7 (CASP7), which belongs to a family of

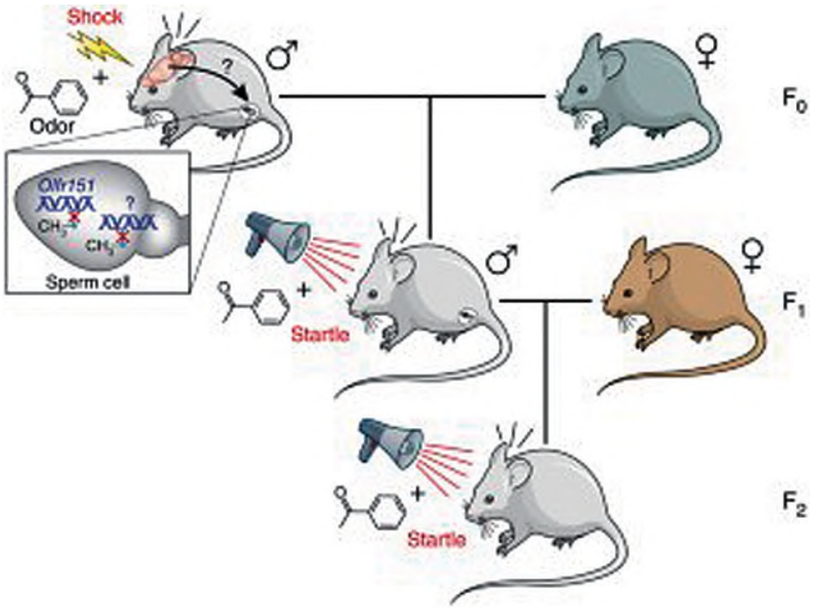


**Figure 6:** *Model for epigenetic inheritance of odor fear conditioning. Association of acetophenone odor with an electrical shock condition the mouse for an enhanced acetophenone startle response of acetophenone Although the mechanism is unknown, this may trigger the release of circulating molecule(s), such as sRNAs or glucocorticoids, that act on spermatogonia to direct DNA methylation changes in both specific olfactory receptor genes, such as Olfr151, and other genes, as yet unknown, that are involved in the fear conditioning circuitry in the brain. When the demethylated sperm fertilizes a naive female, the methylation pattern is maintained in the fertilized eggs and may guide the differentiation of fear circuitry. The adult F1 mouse exhibits enhanced startle in the presence of acetophenone. During primordial germ cell differentiation in the F1 mouse, the methylation pattern triggered by the conditioned exposure to acetophenone is preserved. When the resulting marked sperm fertilizes a naive mouse, the offspring F2 will develop the same conditioned fear response circuitry in the brain, using the epigenetic information in the F1 sperm to guide differentiation. The adult F2 mouse likewise shows a heightened startle response in the presence of acetophenone. The whole Figure and the text were taken from [28]*

**Рисунок 6** – *Модель эпигенетического наследования условного рефлекса страха на запах. Ассоциация запаха ацетофенона с ударом электрического тока обусловливает у мыши усиленную акустическую стартл-реакцию на ацетофенон. Хотя механизм неизвестен, это может вызывать высвобождение циркулирующих молекул (например, микроРНК или глюкокортикоидов), которые действуют на сперматогонии, направляя изменения метилирования ДНК как в специфических генах обонятельных рецепторов (например, Olfr151), так и в других, пока неизвестных генах, вовлеченных в нейронную цепь обуславливание страха в головном мозге. Когда деметилированный сперматозоид оплодотворяет наивную самку, паттерн метилирования сохраняется в оплодотворенных яйцеклетках и может направлять дифференцировку нейронной цепи страха. Взрослая мышь F1 демонстрирует усиленную реакцию испуга (вздрагивания) в присутствии ацетофенона. В ходе дифференцировки примордиальных зародышевых клеток у мыши F1 паттерн метилирования, индуцированный выработанным воздействием ацетофенона, сохраняется. Когда полученный меченый сперматозоид оплодотворяет наивную мышь, потомство F2 развивает ту же выработанную цепь реакции страха в мозге, используя эпигенетическую информацию в сперме F1 для направления дифференцировки. Взрослая мышь F2 аналогично проявляет усиленную стартл-реакцию в присутствии ацетофенона. Рисунок и текст заимствованы из [28]*

proteins that play a central role in cell apoptosis. Site cg14117527 is annotated to RAB43/ISY1-RAB43 (RAB43 is involved in membrane trafficking pathways and cellular homeostasis and is a member of the RAS oncogene family, and the ISY1-RAB43 readthrough transcript) and cg14832449 is annotated to RP11- 1028N23.3, which is a long non-coding RNA [29].

Most DMPs showed the same directionality in DNAm change across germline, prenatal, and direct exposures, suggesting a common epigenetic response to violence. It should be noted that accelerated epigenetic aging is thought to correlate with accelerated biological aging and may be an underlying mechanism for age-related health outcomes [30].

From the point of memory transfer the results of McConnel who performed his experiments with planaria and memory transfer[2] and more recent results obtained with *Aplysia* [31], are pointing to the epigenetic mechanism. Recently [31] the authors reported that RNA extracted from the central nervous system of Aplysia given long-term sensitization training induced sensitization when injected into untrained animals. Furthermore, the RNA-induced sensitization, like training-induced sensitization, required DNA methylation.

The author itself did some research in the memory transfer occurring after the heart transplants [32]

In other words, Darwin's gemmules are present everywhere: "We cannot fathom the marvelous complexity of an organic being; but on the hypothesis here advanced this complexity is much increased. Each living creature must be looked at as a microcosm—a little universe, formed of a host of self-propagating organisms, inconceivably minute and as numerous as the stars in heaven." [1].

How is epigenetic information transferred across generations [33]? The authors do not clarify the mechanisms; however, they are pointing to the "narrow" difference between transgenerational and intergenerational effects: In mammals, transgenerational effects, particularly those that occur in response to the environment, are defined as any phenotypic or molecular effect that persists for 3 or more generations through the female line or 2 or more generations through the male line. By contrast, effects that only persist for 1 or 2 generations are for the most part referred to as intergenerational effects. This definition of intergenerational effects includes, but is not limited to, multiple examples of effects that were classically referred to as parental effects. Whether a phenotype is intergenerational or transgenerational was originally determined by whether the genetic material for the subsequent generations was present at the time of exposure to the altered environment. This often differs between different species, so caution must be used to identify whether the germ cells were present at the time of exposure. The original distinction between these two terms lies in the fact that intergenerational effects could, in principle, be caused by the effects of the parent's environment/physiology directly on the developing embryo/fetus or on germ cells but transgenerational effects could not be due to direct exposure. However, mechanistic investigations of multiple different intergenerational effects have since discovered mechanisms of intergenerational regulation that are not due to the direct effects of the environment on germ cells or F1 embryos. In some cases, these mechanisms are initiated and maintained using similar mechanisms as transgenerational effects such as the transmission of small RNA molecules via germ cells. Nonetheless these effects remain described as intergenerational effects. Thus, the currently used definition of intergenerational has evolved to refer mainly to the duration a phenotypic effect persists for rather than the potential mechanism by which the effect is mediated (*Figure 7*). By comparison, for a phenotype to be considered transgenerational, none of the individual's genetic material can be present at the time of the environmental insult (*Figure 7*). Thus, transgenerational effects predominantly refer to phenotypic effects that persist for three or more generations. The author is not interested in polemics; however, one must admit that the "intergenerational" effects (persisting for 1 to 2 generations) must somehow be incorporated into the germ cells. We are not talking about "classical" Mendelian rules but epigenetic "hereditary" changes.

According to Yap and coworkers [34], small non-coding RNAs constitute a dynamic epigenetic layer in mature (human and mouse) spermatozoa that can exert transgenerational regulatory functions. The profile of these RNAs changes dramatically during spermatozoa maturation. The majority of intracellular small RNAs during early spermatogenesis are miRNAs and piRNAs. In mature spermatozoa, tRNA- and rRNA-derived fragments (tRFs and rRFs, respectively) are the predominant forms, primarily delivered from the epididymis via extracellular vesicles (*Figure 8*). Diet, exercise, and environmental exposures have a direct effect on small RNA levels in spermatozoa, and this differential abundance can reprogram the development of the embryo. Offsprings of fathers with different lifestyles can have different phenotypes, including altered metabolism or behavior. Therefore, small RNAs in spermatozoa are emerging as an important epigenetic layer in development and transgenerational inheritance.

Is the human sperm "sncRNAome" constant or is it variable among ethnic groups? It has been shown [35] that human sperm sncRNAome has a "core component" that shows small variations and a "peripheral component" that shows significant variations across individuals and ethnic

[2] Omary A. Is Memory Transfer Possible? One small creature's surprising role in the study of memory. Psychology Today. 2022. October 12. URL: https://www.psychologytoday.com/us/blog/natured-nurture/202210/is-memory-transfer-possible (date: 13.05.2025).

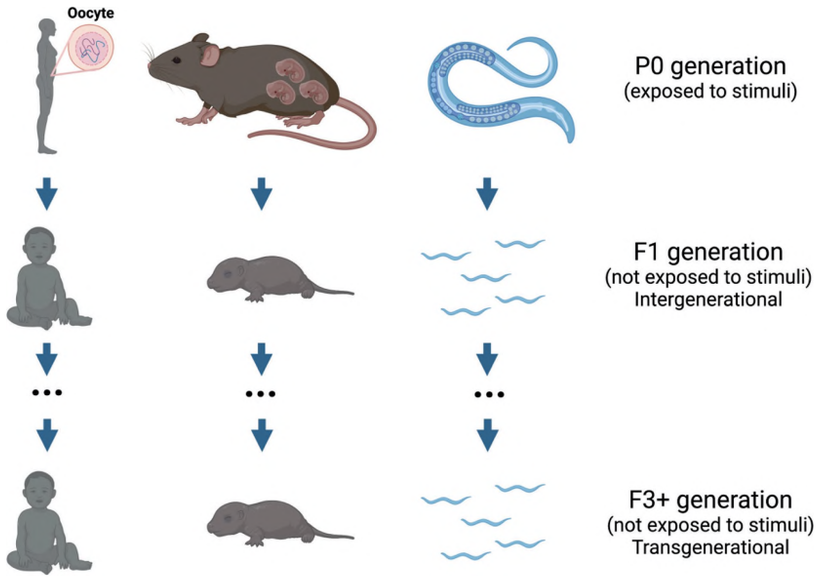


**Figure 7:** *Distinction between inter and transgenerational phenotypes. Numerous different parental (P0) stresses can have multigenerational effects on offspring. Intergenerational effects represent any effect of parental stress on F1 progeny that either directly acts on or is communicated through P0 germ cells or developing F1 embryos in utero. By comparison, all effects that are initiated in the P0 generation and persist into the F3 (or later) generations are transgenerational effects. Effects that are initiated in the P0 generation and persist to the F2 generation are intergenerational if any germ cells of F1 animals have formed in utero when the initiating event/stress was present and transgenerational if no F1 germ cells have formed. These original distinctions between intergenerational and transgenerational effects in F2 progeny are still used as definitions in literature irrespective of the mechanisms that mediate multigenerational effects in progeny, including cases where such effects might not be transmitted via germ cells. The whole Figure and the text were taken from [33]*

**Рисунок 8** – *Разграничение интергенерационных и трансгенерационных фенотипов. Многочисленные различные стрессовые воздействия на родительское поколение (P0) могут оказывать многопоколенные эффекты на потомство. Интергенерационные эффекты представляют собой любые эффекты родительского стресса на потомство F1, которые либо непосредственно воздействуют на зародышевые клетки P0 или развивающиеся эмбрионы F1 in utero, либо передаются через них. Трансгенерационные эффекты – все эффекты, инициированные в поколении P0 и сохраняющиеся в поколениях F3 (или позднее). Эффекты, инициированные в поколении P0 и сохраняющиеся до поколения F2, считаются: интергенерационными, если формирование зародышевых клеток у особей F1 происходило in utero во время действия инициирующего стрессового фактора; трансгенерационными, если формирование зародышевых клеток F1 еще не началось. Эти исходные различия между интергенерационными и трансгенерационными эффектами у потомства F2 продолжают использоваться в качестве определений в литературе, независимо от механизмов, опосредующих многопоколенные эффекты у потомства, включая случаи, когда такие эффекты могут передаваться не через зародышевые клетки. Рисунок и текст заимствованы из [33]*

populations. Thus, the availability of the normal human sperm sncRNAome would help delineate biologically meaningful variations from sample-to-sample natural/random variations.

**Epigenetic inheritance.** In an exciting paper [36], the authors have shown that the epigenetic phenomenon (suppression homozygous mutation for short antennae} occurs in the short antennae (*sa*) mutation of the flour moth (*Ephestia kuehniella*). The authors demonstrated that it is probably determined by a small RNA (e.g., piRNA, miRNA, tsRNA) and transmitted in this way to subsequent generations through the male and female gametes. The observed epigenetic change canceled sa mutation and created a wild phenotype (a moth that appears to have no mutation). It persisted for many generations – up to 40 recorded generations. This epigenetic transgenerational effect (suppression homozygous mutation for short antennae) in the flour moth is induced by changes during ontogenetic development, such as increased temperature on pupae development, food, different salts in food, or injection of RNA from the sperm of already affected individuals into the eggs. The male flour moth does not only deposit sperm into the female, but a spermatophore that contains also other components. These components were separated and injected separately into the fertilized eggs. The components without RNA content (products of accessory glands, spermatophore

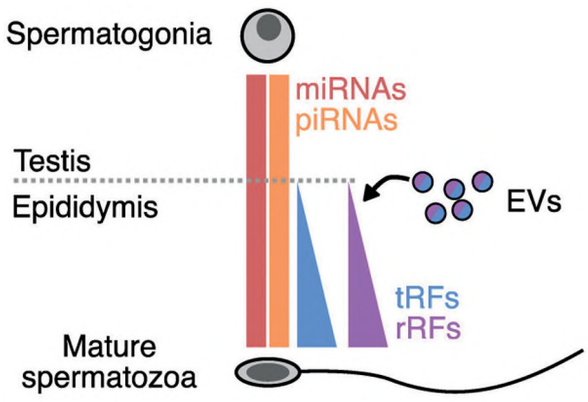


**Figure 8:** *Relative levels of small non-coding RNA as spermatogonia differentiate to mature spermatozoa. As they pass through the epididymis, spermatozoa are loaded with small non-coding RNAs from extracellular vesicles derived from epididymal cells. The whole Figure and the text were taken from [34]*

**Рисунок 8** – *Относительные уровни малых некодирующих РНК в процессе дифференцировки сперматогониев в зрелые сперматозоиды. При прохождении через придаток яичка сперматозоиды насыщаются малыми некодирующими РНК из внеклеточных везикул, происходящих из клеток придатка. Рисунок и текст заимствованы из [34]*

sac, homogenized sperm denatured with ribonuclease) separated from male sperm did not have analogous impact like components with RNA. The effect of total RNA differed from all additives without RNA.

Recently it has been shown [37] that *germline* small RNAs in plants and mammals are heavily pseudouridylated. Piwi-interacting RNAs in mouse testes, are enriched for pseudouridine (Ψ) too. Why are germline small RNAs so heavily modified in both plants and mammals? An intriguing possibility is that modifications of RNA in the germline may avoid viral surveillance systems after fertilization, which could otherwise recognize inherited small RNAs as 'nonself' [38].

Pseudouridine (Ψ) is a C–C glycosidic isomer of uridine (U) with a distinct structure, in which the uracil base is covalently attached to the ribose ring through a C5–C1 linkage, as opposed to the N1–C1 bond found in canonical uridine. This structural alteration substantially affects the physicochemical properties of Ψ, altering its base-stacking interactions and hydrogen-bonding patterns within the RNA helix [39, 40]. As the most abundant post-transcriptional modification, Ψ is widely distributed in various types of RNA, including mRNA, tRNA, ribosomal RNA (rRNA) and small nuclear RNAs (snRNAs). Its unique chemical structure enables it to influence the stability, structure and function of these RNAs, thereby having crucial physiological and pathological roles.

Notably, the Ψ derivative N1-methylpseudouridine (m1Ψ) has been applied in the two approved COVID-19 mRNA "vaccines" (Pfizer–BioNTech and Moderna). Like Ψ, m1Ψ may promote readthrough of endogenous termination codons, the two vaccine mRNAs had two or three consecutive stop codons to mitigate this unwanted effect [41]. However, a recent study found that m1Ψ-modified mRNA translation can lead to the formation of frameshift proteins [42]. The accumulation of Pfizer–BioNTech "vaccine" after vaccination has been shown mainly in the spleen and ovaries[3].

The activities such as "Decoding the Spermatogenesis Program: New Insights from Transcriptomic Analyses" [43] clearly showed a more detailed approach to the to the transcriptome (i.e., RNA expression levels of all genes) at tissue and cellular levels.

And, in concert to the previously mentioned results the attempts to find the testicular gene expression are continuing at "higher" level [44]. In principle, spermatogenesis is a multi-step biological process where mitotically active diploid (2n) spermatogonia differentiate into haploid (n) spermatozoa via regulated meiotic programming. The alarming rise in male infertility has become a global concern during the past decade thereby demanding an extensive profiling of testicular gene expression. Advancements in Next-Generation Sequencing (NGS) technologies have revolutionized our empathy towards complex biological events including spermatogenesis.

The authors [44] are illustrating the possible applications of Sc-RNA-Seq data towards framing appropriate preclinical studies (both in vitro and in vivo approach) leading to potential future diagnostic (assays/tools/kits) in male reproductive health car.

**Bioweapons.** In the last section the author is possibly approaching to open the box of Pandora's. However, the preparedness for future scenarios is well-grounded [45, 46].

It has been shown[4] that after the vaccination with Pfizer–BioNTech "vaccine" (with fully

[3] SARS-CoV-2 mRNA Vaccine (BNT162, PF-07302048). URL: https://www.docdroid.net/xq0Z8B0/pfizer-report-japanese-government-pdf#page=17 page 17 (date: 13.05.2025).

[4] URL: https://lowtoxinforum.com/threads/help-with-understanding-pfizer-report-accumulation-of-vaccine-in-ovaries.41792/ (date: 13.05.2025).

substituted uridine with the derivate N1-methylpseudouridine (m1Ψ)) the accumulation of the "vaccine" has been mainly observed in the spleen and the ovaries. Paradoxically, there is rather low accumulation of the "vaccine" in the testes. It should be noted that pseudouridine guides germline small RNA transport and epigenetic inheritance [37].

It is of interest that the number of newborns in Czechia (population 10.6 million) dropped from 110,200 (in 2020) to 84,311 (in 2024)[5], in Hungary (population 9.6 million) dropped from 92,338 (in 2020) to 77,511 (in 2024)[6], and in Slovakia (population 5.4 million) dropped from 56 650 (in 2020) to 46 241 (in 2024)[7]. In Poland (population 37.6 million) the number of births in 2024 (252 000 which is over 20 000 less than in the year 2023) was the lowest since the end of World War II[8]. So far nobody knows if this has been a vaccination "side effect" or an aim of vaccination with mRNA preparates in the sense of depopulation. So far nobody publicly announced the reason(s) for this "experimental fact".

On the other hand, we were describing an existing enormous interest of human sperm sncRNAome (*Figure 8*) and testicular single cell RNA (Sc-RNA-seq) data. In other words, huge libraries of all sperm RNAs are created. Interestingly, one can clearly see the ethnic differences between races [35]. This can be the tip of an iceberg of more deeply and precisely derived data coming from different subgroups and from different inhabited areas. Today with the introduction of powerful AI or "deep learning technologies" it is not difficult to extract the data from the sperm sncRNAome and to introduce so called "sRNA harm".

In the previous text we have shown that the acquired F0 mice to odor fear conditioning before conception can be transmitted to F1 and F2 generations which have an increased behavioral sensitivity to the F0-conditioned odor but not to other odors. So, one among the different possibilities is to introduce a "heritable" sterility. There will be a slow decline of the number of newborns in the first (F1) generation which will further proceed to sterility of F2 or F3 generations. At this time, it will be too late to analyze the reason for these changes. One should not doubt such approaches. The employment of every day growing power of tools such as AI or deep learning technologies in the "right hands" can bring extremely 'interesting" results with astonishing speed. And, taking in account the stability and nucleotide number ("shortness") of sRNA which are heavily pseudouridinylated, one can establish a rather cheap mass production. Such products can be added to each vaccine or nucleic acid (mRNA or DNA) preparate ("vaccine") or can be distributed with food products and with aerosols. It should be noted that all mRNA (DNA) preparates are using LNP (lipid-based nanoparticles) technology. The presence of PEGylated lipids in LNPs extends their circulation time in vivo [12]. Moreover, their size corresponds to the size of EV ("Darwin's gemmules") [12]. The process of fusing of these LNP is known in the laboratory praxis as the transfection. This means that the whole LNP cargo is directly transported to the cell cytoplasm. It appears that the technology for altering epigenetic inheritance is ready.

**Conclusion.** Hijacking epigenetic mechanisms of gene control for targeted *in vivo* manipulation of gene expression has tremendous potential for treating diseases and catalyzing regenerative medicine [47]. CRISPR-based epigenome editing offers a more precise approach to treat a wider range of disorders stemming from diverse forms of epigenetic dysregulation. These include diseases resulting from gene overexpression, duplication or loss of expression as well as complex alterations such as haploinsufficiency, X-linked inheritance, imprinting disorders and promoter and enhancer mutations [47, 48].

However, current research has not yet yielded epigenetic inheritance technologies with proven capability to intentionally alter the phenotype of human offspring. The significant scientific focus on human sperm miRNA and single-cell RNA sequencing (Sc-RNA-seq) of testes is leading to the rapid accumulation of data and the creation of vast libraries of spermatozoal RNAs. Initial analyses of these datasets suggest the presence of population-specific variations. However, the functional significance, biological relevance, and

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ethical implications of these observed differences remain largely unexplored and require rigorous investigation.

Separately, studies on the biodistribution of mRNA vaccines, such as the one from Pfizer–BioNTech, have reported accumulation in reproductive tissues like the ovaries, among others. This warrants ongoing research into the long-term effects of any novel medical intervention on germline cells. Furthermore, complex demographic shifts, such as the population changes observed in the V4 countries, highlight the critical need for robust, multifactorial public health analysis. While the direct causation with any single factor like vaccination is unproven and highly speculative, these real-world trends underscore the importance of developing advanced monitoring systems. In general, without exaggeration, epigenetic gene control is one of the most complex and alarming ethical and strategic problems humanity faces alongside the development of biotechnology. The described mechanisms are not science fiction. Epigenetic inheritance involving small RNAs is an established scientific fact, proven in animal experiments. The ability of external factors (diet, stress, toxins) to cause heritable epigenetic changes is also confirmed. Therefore, the hypothetical possibility of creating an agent that deliberately induces such changes becomes less hypothetical with each passing year. The consequences of their application may not be immediate, but manifest a generation(s) later. The first victims of exposure could merely be "carriers" of the pathology for their children. Detecting such an attack would be extremely difficult, and the consequences, embedded in the epigenome, could be irreversible. Theoretically, one can also imagine agents targeting specific epigenetic markers characteristic of certain ethnic or population groups. This makes it possible to create a tool for "silent" depopulation. It is not impossible that such tools have already been created. In the case of interference with the epigenome that affects germ cells, any error (off-target effects) would be perpetuated in subsequent generations.

This problem is a systemic challenge on par with the nuclear threat of the 20th century, but potentially more insidious. An urgent and broad public discussion is required, involving not only scientists and politicians but also philosophers, ethicists, and the whole of society. It is necessary to develop new ethical norms and control mechanisms that would not hinder science but guide it exclusively toward peaceful and responsible use. Ignoring these risks in the hope that "this is still a long way off" is an extremely irresponsible position.

***Limitations of the study / Ограничения исследования***

All data were obtained from public sources; therefore the article is strictly limited on these public sources only. / Все данные получены из открытых источников, поэтому статья строго ограничена только этими открытыми источниками.

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***Autor' Contribution / Вклад автора***

Elaboration of the concept of the paper; collection, analysis, and systematization of scientific literature; writing and edition of paper / Разработка концепции статьи; сбор, анализ и систематизация научной литературы; написание статьи.

***Author's statement / Заявление автора***

I am declaring that I prepared the article from sources freely available on the Internet and free available publications, figures, and other possible legal sources. I, as a sole author declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest / Я заявляю, что подготовил статью из источников, находящихся в свободном доступе в Интернете, а также свободно доступных публикаций, рисунков и других возможных легальных источников. Я, как единственный автор, заявляю, что исследование проводилось при отсутствии каких-либо коммерческих или финансовых отношений, которые могли бы быть истолкованы как потенциальный конфликт интересов.

***Peer review information / Сведения о рецензировании***

The article has been double-blind peer reviewed by two experts in the respective field. Peer reviews are available from the Editorial Board and from Russian Science Citation Index database. / Статья прошла двустороннее анонимное «слепое» рецензирование двумя рецензентами, специалистами в данной области. Рецензии находятся в редакции журнала и в РИНЦе.

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