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Review

On the Role of Seminal Fluid Protein and Nucleic Acid Content in the Paternal Epigenetic Inheritance

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Abstract: The evidence supports the occurrence of environmentally induced paternal epigenetic inheritance shaping the offspring phenotype in the absence of direct or indirect paternal care, and the empirical results clearly indicate that sperm epigenetics is one of the major actors mediating these paternal effects. However, sperm often make up only a small fraction of the male ejaculate in animals. Males also have a complex mixture of proteins, peptides, types of small RNAs and cell-free DNA fragments in their seminal fluid. These molecules are in close contact with reproductive cells, tissues, organs and other molecules of both males and females during reproduction. Moreover, their production and use are very sensitive to environmental conditions which makes them potential modulators of environmentally and developmentally induced paternal effects on next generation(s). Although there is some intriguing evidence of seminal fluid mediated paternal epigenetic effects, the underlying molecular mechanisms remain poorly defined. In this review, I discuss the current evidence regarding the association between seminal fluid and environmentally induced paternal effects, and the possible trajectories and the mechanisms which seminal fluid can involve to mediate paternal epigenetic inheritance.

Keywords: seminal fluid; seminal plasma; epigenetics; transgenerational plasticity; sperm; paternal effects

1. Introduction

Epigenetic mechanisms including DNA methylation, histone modification, and transmission of small RNAs (i.e., non-coding small RNA molecules; sRNAs), and their functions in genome regulation and cell-to-cell transmission, are not being considered as revolutionary subjects in today's biology research. Organisms encounter varying external and internal environmental conditions altering their phenotypes which are regulated by these epigenetic mechanisms over developmental and lifetime. However, the heritability of epigenetically acquired phenotypes via the transfer of alternative functional states of these mechanisms to the next generations is a hot topic [1–5], which, I believe, will soon lead to an explosion of new analytical approaches in the various aspects of evolutionary biology and heredity research [6–11]. In the same way as in the genes, epigenetic variation occurs within populations that can be transmitted across generations [1,12,13]. Thus, there is now a greater effort in constructing conceptual frameworks of Extended Heredity considering the inheritance of epigenetically acquired phenotypes [14–18]. Furthermore, increasing number of empirical studies have been focusing on mechanisms of epigenetic inheritance, especially on the role of female and male germline [19–21].

Studies of paternal epigenetic inheritance through sperm cells indicate the significant role of sperm epigenetic status in the alteration of the offspring phenotype in an adaptive or maladaptive way [22–31]. On the contrary, paternal effects through factors other than sperm epigenetics were generally assumed to be absent or less important in the absence of conventional paternal care in which the male role is often thought to be limited by transferring his DNA to offspring [15,32]. Apart from sperm, males transfer a complex mixture of varying molecules (e.g., lipids, carbohydrates, water etc.) and microbes in the

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seminal fluid during mating [33,34]. Notably, the seminal fluid also contains a number of proteins, peptides, sRNAs, and cell-free DNA (cfDNA) fragments that closely interact with male reproductive tracts and sperm, as well as female reproductive tracts and molecules, and eventually eggs and embryos. Furthermore, studies have explicitly revealed in many taxa that seminal fluid composition exhibits high plasticity in responding to varying environmental factors [35–44] and is also subjected to the interaction between genotypes and environments [45,46]. Therefore, seminal fluid protein and nucleic acid (*here after referred as seminal fluid for simplicity*) contents could play a more significant role in epigenetic inheritance and mediating environmentally induced paternal effects on next generations than has hitherto been suspected [14,47–52].

In this mini review, I focus on the evidence of seminal fluid-mediated paternal effects on offspring and discuss the proximate mechanisms of seminal fluid within the concept of transgenerational epigenetic inheritance (i.e., inheritance of variations to the next generations that are not derived from differences in the DNA sequence [2,53]). Note that, I prefer to use the term *epigenetic inheritance* instead of *transgenerational epigenetic inheritance* because it is a much broader term including mechanisms of both cell-to-cell and (grand)parent-to-(grand)offspring transmissions and seminal fluid-borne epigenetic inheritance mechanisms may comprise both. I also rather chose not to use the term *nongenetic inheritance* while referring to any parental effect that derived from one or more of those defined epigenetic mechanisms. In fact, *Epi* is a prefix in Greek often used to refer something "*upon*, *on*, *over*, *near* or *at*" of something else, and rarely used to refer something "*beyond*" something else. Indeed, epigenetic mechanisms tightly work *with*, *on* or *near* the genes throughout the genome, therefore I believe that terms such as *nongenetic inheritance* are confounding and cause confusion about the concept of epigenetic inheritance.

2. Association between seminal fluid and the offspring phenotype

The most supportive evidence of the link between environmentally induced seminal fluid composition of the father and the phenotype of the offspring comes from a few recent studies. Some of these studies used a sort of double-mating assay where a female mates with two males in turn or receives a mix of two males' ejaculates, and estimated seminal fluid-mediated effects by decomposing sources of own or step offspring phenotypic variance. In their seminal study, Crean et al. (2014) used a so-called telegony approach in the neriid flies *Telostylinus angusticollis* where the female mates with two conditionally manipulated males, and the effects of first male's condition on step-offspring phenotype (i.e., body size in their study) is estimated [54]. In their experiment, females received sperm and seminal fluid of first male that were raised in different nutritional conditions (either high- or low-quality) before the time of full maturation. The second mating took place after females became mature; therefore, the second male sired a large majority of the offspring. Afterwards they tested for the relationship between the first male condition and step-offspring body size and found that body size was influenced significantly by the condition of the first male indicating an effect derived from seminal fluid of first males. Although they did report no direct paternal effect, because it was seen in step-offspring, the seminal fluid effect on the body size of the subsequent generation cannot be overlooked as a potential mediator of epigenetically acquired phenotype.

Using the similar approach in the red flour beetles *Tribolium castaneum* that seminal fluid of the males exposed to bacterial infection were used as one of the two males mated with the female, it has been shown that step-offspring immune resistance is altered by seminal fluid of exposed males [55]. The associations between paternal diet and metabolic dysfunction in offspring have been also shown repeatedly in mice that are mediated either by sperm-borne or seminal fluid-borne processes [56–58]. In another study using artificial ejaculation in European whitefish *Coregonus lavaretus*, the existence of foreign seminal fluid in the ejaculate has been shown increases the swimming performance of the offspring [59].

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Similar experimental settings were also used to measure embryo survival as the observed offspring phenotype that could be affected by seminal fluid. For example, the variance in embryo viability is partially explained by seminal fluid composition in the cricket *Teleogryllus oceanicus* [60], and seminal fluid of males on low protein - high carbohydrate diet decreased the embryo viability [61]. These results undoubtedly indicate an association between seminal fluid composition and the reproductive success of seminal fluid donors; however, these results need to be cautious while interpreted within the scope of paternal effect to the inheritance of a fitness trait, indeed population of interest has died before data collection.

Another line of studies has particularly focused on the effect of the absence of seminal fluid, or its producing and storage organs. These studies often result in a lack of fertilization or embryo growth [59,62–67], however, some of them have clearly indicated the changes in the phenotypes of the offspring in the absence of seminal fluid. For example, the ablation of the seminal fluid content by removing organs affected the metabolic health of male offspring in mice [68] and caused developmental and behavioral changes in offspring of golden hamsters [69,70]. In the fruit flies *Drosophila melanogaster*, it has been shown that females that received seminal fluid had daughters with higher fertility compared to females did not receive [71]. Moreover, when two males from different populations were mated with a female in *D. melanogaster*, an enhanced fecundity of stepdaughters was shown due to the effects of seminal fluid and mother interactions [72].

3. The potential mechanisms of seminal fluid-mediated paternal epigenetic inheritance

As mentioned above, there is now compelling evidence of seminal fluid-mediated paternal effects occurring, and furthermore, considering the examples come from a wide range of taxa such as insects, fishes, and mammals, they can be widespread among animals. It would be also not surprising that seminal fluid could have unique pathways which have the capacity to act epigenetically. Because, unlike the majority of other organic molecules, seminal fluid is in close contact with several reproductive tissues, and germ cells in both sexes and eventually somewise reaches to embryos. In this framing, seminal fluid can have at least three different routes, though they are likely to be interrelated, to control environmentally induced paternal epigenetic inheritance. The confined studies in the area of epigenetics research provide key ideas into the mechanistic questions by showing seminal fluid is capable of altering epigenetic status of (1) sperm, (2) female reproductive tracts, (3) eggs and embryos, as discussed below.

3.1. Seminal fluid mediates sperm epigenetics

The sperm epigenetic pattern and its role in the formation of offspring health and phenotype are now well known [23,28,29,73]. DNA methylation, histone modification, and sRNA contents of sperm are the best-established epigenetic mechanisms [22,23,53,74–78] that can be stable and heritable across generations [22,79–81]. The environmental conditions such as nutrition, toxins, social, stress, temperature, etc. alter these epigenetic mechanisms, which are incorporated into the sperm and transferred into the embryo that controls and modifies changes in embryonic development and/or adulthood of the offspring [56,57,82–84]. Therefore, considering seminal fluid is produced and used depending on such environmental conditions while in close contact with sperm in the time between meiosis and ejaculation, its contribution to sperm epigenetic modifications based on conditions do seem inevitable.

First of all, there is substantial evidence linking seminal fluid content to the control of sperm RNA composition. In animals, seminal fluid carries various kinds of extracellular vesicles (e.g., micro- and nano-vesicles, exosomes, etc.) that contain different molecules including proteins, peptides, mRNAs, and sRNAs [85–91], and this cargo has many essential functions for sperm fertilization success [87,88,91–97]. These extracellular vesicles of seminal fluid can be transferred between cells and tissues, and release their content to a

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targeted cell [98–101]. For example, in mammals, seminal vesicles and epididymis - tissues where some seminal fluid contents are produced and secreted - origin vesicles can attach to the sperm membrane and release their content to sperm [100,102]. As a matter of fact, seminal fluid is known to be able to adjust small non-coding RNA composition of the sperm by transferring a variety of sRNAs within the extracellular vesicles, as well as, as free molecules in the plasma [22,91,100,103–106]. Moreover, there are also cell-free DNA fragments [107,108], mRNAs, RNAases, and double-stranded RNAs in seminal fluid [109–112]. Recent findings showed that the mature sperm has also permeability to take exogenous DNA [113–115], as well as capacity to internalize the mRNA to DNA through reverse transcriptase [116]. The exposed somatic cells communicating their exposures to the germline through the transfer of extracellular vesicles can induce changes in offspring [23,106,117–120]. For instance, in mice, seminal fluid-originated extracellular vesicles mediating the sRNAs in sperm cause a persistent transmission of paternal stress conditions that alters transcriptomic patterns in offspring [121]. The artificial injection of testis-specific sRNAs to one-cell embryo also shown as mediates paternal effects of diet-induced obesity and metabolic disorders [122]. Furthermore, it is also known that the production of seminal fluid vesicles and their cargo, as well as free protein and peptide composition are adjusted depending on various environmental conditions [35–44,123–125]. Therefore, a novel role seems plausible that seminal fluid to be a messenger collecting information from other tissues and transferring it to sperm that are embedded into forms of nucleic acids to modify sperm epigenetic status that can ultimately shape offspring phenotype [23,119,120].

The level of seminal fluid gene expression and/or abundance of a specific protein in the seminal fluid can be also related to sperm epigenetics. For example, the expression level of *Heat-Shock Protein* coding genes depending on population density were found to be related with change in offspring morphology in a locust *Locusta migratoria*, and that HSP level was suggested as a potential mechanism of paternal epigenetic regulation and maintenance of transgenerational plasticity [126,127]. Supporting the notion that some HSP proteins were commonly identified in the seminal fluid which are also transferred to female in fruit flies *Drosophila melanogaster* [128,129], the red flour beetle *Tribolium castaneum* [130], boars [131] and human [132], a potential role of seminal fluid HSPs in epigenetic inheritance is obtainable.

There is also a potential of seminal fluid-mediated DNA methylation and chromatin modification of the sperm genome. Such epigenetic modifications in sperm often occur prior to ejaculation in which sperm cells are stored often with seminal fluid content in the storage organs [73]. For example, the absence of glands producing seminal fluid disturbs epigenetic reprogramming by affecting histone acetylation in the sperm of golden hamsters [69]. The exposure to toxicants in seminal fluid is associated with spermatozoa DNA hyper- or hypo-methylation in human [133]. Interestingly, seminal fluid was shown associated with the zinc profile of sperm chromatin which is controlling chromatin stability in mammals [134,135].

On the other hand, the genes responsible to produce seminal fluid contents are themselves could be also subject to specific DNA methylation and/or histone modification patterns, since many genes are expressed at the appropriate time and levels are required in male reproductive organs producing seminal fluid contents. For example, DNA methylation profiling of the seminal vesicles, where some seminal fluid contents are produced in mouse, following a toxicity exposure affects developmental reprogramming at adulthood has been shown by using genome-wide transcriptome and DNA methylation profiling of the seminal vesicles [136]. A very interesting study found that the methylation level of some testis-specific promotors within cell-free DNA is highly correlated to the methylation level of promoters in the testicular tissues [108]. Moreover, the cell-free DNA fragments were shown as a potential courier for DNA methylation pattern of testis and epididymis-specific gene promoters in human semen [137]. In point of fact, this association suggests that seminal fluid has the potential to preserve and carry the information for DNA methylation pattern of specific genes related to seminal fluid production.

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As evidence has pointed out, seminal fluid may have different routes to mediate sperm epigenetics, and these eventually affect offspring phenotype, therefore can be considered within the scope of epigenetic inheritance. The novel idea that the paternal environment can affect offspring through mechanisms involving the transfer of information between seminal fluid and sperm via seminal fluid protein, peptide, and nucleic acid contents is a very promising and exciting hypothesis. However, the mechanism of how seminal fluid factors are formed in somatic cells, and alters sperm epigenetics, in other words, causality and the details of mechanisms are yet to be explained.

3.2. Seminal fluid mediates female epigenetics

Seminal fluid is transferred to females along with sperm during mating, and its content is capable of causing physiological and behavioral changes in the females [138–144]. Notably, the effects of receiving seminal fluid proteins and peptides have been extensively studied in the model organism *Drosophila melanogaster* including studies that showed changes in female remating latency, receptivity, ovulation, oogenesis, sperm storage and survival, egg-laying rate, and a number of other reproductive functions [142,145–149]. Many of these seminal fluid-mediated effects in females have been also defined in many other species [34,146,150–157]. The most plausible mechanism explaining female manipulation via seminal fluid is that seminal fluid causes a change in gene regulation in females which indeed alters the epigenetics of the female. Females show transcriptional responses to mating [158], and several gene expression studies have repeatedly found evidence of seminal fluid-mediated gene regulations in mated females in *D. melanogaster* including genes related to egg development, immunity, nutrient sensing, and behavior [158–161]. A recent study has also showed that receiving seminal fluid triggers a wide transcriptional regulation in female reproductive tissues in mosquitos [162]. Although it is clear that receiving seminal fluid causes transcriptional regulation in females, our knowledge on the mechanisms and pathways of how seminal fluid involves in these processes is scarce.

There is some evidence of the extracellular cargo of seminal fluid containing vectors and molecular signals influences the female epigenetic responses by targeting female tissues and cells [163,164]. For example, seminal fluid contents interacting with cells in female reproductive tracts to initiate immune responses have been widely studied [68,164–172]. Moreover, the exosomes present in seminal fluid are shown as involved in the immune-related gene regulation in the uterus in boars [169]. The male-induced maternal care has been also explored in many animals [26,173] and females can moderate their food intake and investment in eggs and offspring also depending on seminal fluid signals. For instance, effects on female egg investment found in *D. melanogaster* as related to existence of a specific seminal fluid protein (i.e., sex peptide) [174,175]. Other studies showed also that altered maternal investment to egg or placenta affects offspring phenotype. In rodents, the placental phenotypes such as weight and size were found altered by the absence of seminal fluid, and the modified placental composition aroused metabolic dysfunctions in offspring [68]. The testosterone level in the seminal fluid of the chicken *Gallus g. gallus* affects maternal investment to eggs and ultimately offspring body weight [176]. In domestic species, the absence of seminal fluid during artificial insemination were suggested likely related to offspring health problems [139,177]. Overall, the effect of seminal fluid contents that act in the female reproductive tract altering female immune or nutritional responses go well beyond to the induction of successful fertilization, and modify offspring phenotype.

Inevitably, any seminal fluid-mediated maternal environment can affect offspring phenotype predictably from the outcome of maternal epigenetic inheritance research that clearly shows maternal effects on next generations [178–183]. But there are many unanswered questions such as how female plays a role to modify offspring phenotype according to the information comes from males' seminal fluid, what are the mechanisms to convert information into paternally derived heritable epigenetic information, especially which specific proteins or peptides act as signals to transmit paternal information.

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3.3. Seminal fluid mediates egg and embryo epigenetics

Apart from seminal fluid-mediated epigenetic modifications in sperm and female reproductive tracts discussed above, seminal fluid may also directly reach developing or mature eggs and embryos that can affect changes in offspring phenotype. However, we have yet very limited evidence of direct interactions between seminal fluid contents and eggs or embryos. For instance, a study showed the isotope-labeled amino acids of seminal fluid proteins from the ejaculate to be incorporated into eggs in the cricket *Teleogryllus oceanicus* [184]. The direct fusion of seminal fluid content into the egg can cause epigenetic modifications considering their known role and potential mechanisms in modifying sperm epigenetics, however, the existence of seminal fluid content in eggs after insemination remains to be yet demonstrated in other species. On the other hand, the perturbation of seminal fluid altered the histone modification in fertilized oocytes and DNA methylation pattern of embryos in golden hamster suggesting also a direct role of seminal fluid in egg and embryo epigenetic status [69] however its route to reach to eggs or embryo remains unclear.

There are some evidence that sperm delivers not just DNA but mRNA and sRNAs to eggs that could be originated from seminal fluid producing organs [185,186]. For example, one major sperm protein responsible for oocyte maturation in females is provided by sperm to oocytes in extracellular vesicles carried in the seminal fluid has been shown in the model organism *Caenorhabditis elegans* [187]. The sRNAs that are transfer to sperm via seminal fluid are essential for embryonic development in mice have been also shown [106]. Interestingly, the sperm originated sRNAs were identified making the 10% of embryonic RNA that were transferred via sperm into the oocyte upon fertilization in *C. elegans* [188] having important functions such as constituting a memory of gene expression, controlling gene silencing, regulating antiviral immune response in subsequent generations [189–193]. Moreover, the use of injection of testis originated sRNAs to male mice fed with a high-fat diet into one-cell embryos resulted in some pathological phenotypes in the adult offspring that were not observed when sRNAs from healthy control males were used [122]. These evidence suggest seminal fluid could deliver its content using sperm as a transporter that can eventually cause changes in offspring phenotype.

4. Conclusion and future directions

The literature of paternal effects on offspring phenotype, health and fitness is large [15,47,51,194], however, as to my knowledge only a very small part of the studies focused on seminal fluid-mediated effects, and their underlying exclusive mechanisms. As mentioned above, overall evidence has pointed out that seminal fluid mediated paternal effects on offspring phenotypes occur and mediated by or involve in regulations of epigenetic mechanisms. In order to gain a better understanding of the molecular mechanisms of seminal fluid-mediated inheritance, more research is needed on how the acquired environmental message can form heritable information through modifications within the seminal fluid composition. It will, therefore, be of interest to determine the seminal fluid-mediated paternal epigenetic inheritance in different taxa and under different environmental conditions. Further studies are also needed to cover a wide range of different phenotypes in offspring such as life history traits, social and mating behaviors etc. which will also allow to focus on specific pathways of epigenetic mechanisms via seminal fluid. In addition, there is need for comprehensive studies on the occurrence, pattern and inheritance of seminal fluid gene regulation in specific reproductive tissues under different conditions to better elucidate the mechanisms involving seminal fluid-mediated paternal epigenetic inheritance.

As summarized here, a number of studies have shown that protein and nucleic acid contents of seminal fluid which are either freely carried into the plasma or into the extracellular vesicles have great potential mediating paternal inheritance. Therefore, studies including high-throughput seminal fluid profiling of protein, peptide, mRNAs, sRNAs and cell-free DNAs under different environmental conditions are needed that can be used

to test links between offspring phenotype and specific seminal fluid contents. Another very exciting field is represented by the potential role played by the other non-sperm fraction of the seminal fluid such as microbiomes were not discussed in this review. For example, studies on microbiome of the seminal fluid have shown associations between male conditions and seminal fluid microbe composition that could affect offspring during development [195–197].

Experiments are also needed to be carefully designed to estimate seminal-fluid mediated paternal effects and study its mechanisms. First, they need to disentangle factors carried by sperm which are derived independent of seminal fluid from factors related to seminal fluid. The use of animal models such as genetically modified males that can only produce and transfer seminal fluid can help to control for different factors. On the other hand, methods such as artificial insemination that can allow to control of seminal fluid origin can have advantages in studying with ecologically relevant species possibly in their natural context. On the other hand, the confounding genetic effects and female and male interactions must be also controlled while testing for seminal fluid-mediated paternal effect. Especially it is evident that paternally driven maternal effects are an important consideration when designing experiments. Controlling such effects while estimating environmentally induced paternal effects on offspring phenotype, a quantitative epigenetics approach can be very useful to improve study designs [9,10,198].

Going forward, a deeper understanding of the role of seminal fluid and associated environmental factors on paternal epigenetic inheritance will improve critically to the advancement of the fields of evolutionary epigenetics and extended heredity. If selection favors an environmentally induced seminal fluid-mediated phenotype on offspring that maximize seminal fluid-borne benefits, that could therefore be evolutionary adaptive. Considering the well-known rapid evolutionary pattern of seminal fluid proteins and peptides [199–203], to better understand the role of epigenetic inheritance on evolution of seminal fluid proteins can shed light on rapid evolution of reproductive proteins.

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