Review

MOLECULAR METABOLISM

# Sperm epigenetics and influence of environmental factors

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## ABSTRACT

**Background:** Developmental programming of the embryo is controlled by genetic information but also dictated by epigenetic information contained in spermatozoa. Lifestyle and environmental factors not only influence health in one individual but can also affect the phenotype of the following generations. This is mediated *via* epigenetic inheritance i.e., gametic transmission of environmentally-driven epigenetic information to the offspring. Evidence is accumulating that preconceptional exposure to certain lifestyle and environmental factors, such as diet, physical activity, and smoking, affects the phenotype of the next generation through remodeling of the epigenetic blueprint of spermatozoa.

**Scope of Review:** This review will summarize current knowledge about the different epigenetic signals in sperm that are responsive to environmental and lifestyle factors and are capable of affecting embryonic development and the phenotype of the offspring later in life.

**Major conclusions:** Like somatic cells, the epigenome of spermatozoa has proven to be dynamically reactive to a wide variety of environmental and lifestyle stressors. The functional consequence on embryogenesis and phenotype of the next generation remains largely unknown. However, strong evidence of environmentally-driven sperm-borne epigenetic factors, which are capable of altering the phenotype of the next generation, is emerging on a large scale.



**Keywords** Sperm; Spermatozoa; Epigenetic; Epigenetic inheritance; Small RNA; DNA methylation; Histone

## 1. INTRODUCTION

Lifestyle factors such as diet, physical activity, smoking, and alcohol consumption, are well known to influence the predisposition to obesity, type 2 diabetes, cardiovascular disease, and cancer, which represent an extraordinary disease burden worldwide. While one's lifestyle clearly affects health and lifespan at the individual level, recent epidemiological studies have provided evidence that the lifestyle of one generation can modify the risk of developing chronic diseases in subsequent generations through so-called *parental effects*. In fact, the plausible influence of preconceptional environmental factors on the next generations' phenotype is not a new idea. The evolutionary theories of both Jean-Baptiste Lamarck and Charles Darwin have long suggested that, at the population level, environmental factors select for particular phenotypes. However, what represents a paradigm shift is the discovery that parental effects can affect the successive generation's offspring, through mechanisms that seem *independent* from genetic factors. The separate investigation of paternal effects (where the male only is exposed to a specific environment before conception), has provided further evidence indicating that sperm-borne factors responsive to changes in lifestyle can modulate the developmental programming of the offspring by so-called *epigenetic inheritance* — a term referring to the direct modification of the gametic epigenome by the environment and subsequent transmission to the next generation [1].

Environmentally-driven epigenetic modifications of gametes provide a potential molecular basis to explain the transmission of developmental plasticity across generations, as well as a mechanism to understand "missing" heritability factors observed with certain diseases. Indeed, in the context of metabolic diseases, all or part of the unsolved heritability of obesity and type 2 diabetes may be ascribed to epigenetic inheritance. This is supported by the epidemiological observation that food availability in childhood and adolescence influences the risk of developing cardiovascular diseases in the offspring [2]. It should be emphasized that the second- and not the first-generation offspring is affected. Moreover, transmission occurs through the paternal line, thereby circumventing possible maternal or *in utero* effects, which is at the origin of the hypothesis that a non-genetic message is transmitted to the following generations through gametes [2]. Animal models of paternal inheritance have provided definitive evidence that dietary factors introduced before conception can affect the metabolism of the offspring through epigenetic inheritance [3—5]. For example, paternal overnutrition increases body weight, and adiposity and impairs glucose tolerance and insulin sensitivity in adult female offspring [4]. In a follow-up study, using the same animal model of diet-induced obesity in the fathers, high-fat diet feeding reprograms the epigenome of spermatozoa, thereby providing further evidence to support the hypothesis that nutritional factors modify the metabolic phenotype of the offspring through epigenetic inheritance [6]. In humans, nutritional status and physical activity levels were associated with dynamic epigenetic changes in spermatozoa [7—9], providing evidence to hypothesize that lifestyle factors prior to

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conception can modulate the health of the offspring through epigenetic inheritance in humans as well. In addition to nutritional factors, numerous prominent laboratories find that other environmental factors, such as exercise, endocrine-disruptors, as well as traumatic stress, influence the developmental plasticity of phenotypes through epigenetic inheritance (Figure 1) [10–12].

For obvious technical limitations, few studies have investigated the effect of environmental factors on the oocyte epigenome [13,14]. Therefore, this review focuses on the sperm epigenome, about which greater knowledge exists. When addressing epigenetic inheritance experimentally, paternal models are primarily used, as they require less experimental resources and confounding factors are easier to exclude. In models of maternal exposure, environmental factors, even if only present before conception, may later influence the developmental milieu of the embryo (e.g. by altering placental function). This constitutes an important source of bias, as the resulting phenotype of the offspring might be affected by gametic influences, and observed effects may simply be of pure *inter*generational origin as compared to *trans*generational. In addition, both F1 *and* F2 generation are under maternal influence during *in utero* development, as the germ cells of F1 are developing at the embryonic state. Consequently, to determine the effect of *in utero* exposure on epigenetic inheritance in a transgenerational fashion, investigations need to be extended to the F3 generation (Figure 1) [5]. However, it is sufficient to study the F2 generation in paternal models, as the aforementioned *in utero* influences are not at play.

Paternal models are not void of possible confounding factors, however, and are not self-sufficient to prove gametic inheritance (Figure 1). For example, it is speculated that contamination of maternal microbiota by the male at time of mating may impact the *in utero* environment [15]. In addition, the seminal fluid may send signals to the maternal tract and ultimately affect embryo development (reviewed in [16]). Approaches using *in vitro* fertilization (IVF) may represent a gold standard, with several groups successfully replicating respective parental effects by IVF/ICSI or microinjection [10,17–20]. However, caution should be applied when interpreting results from studies using prior handling of gametes, as the procedures themselves may induce significant epigenetic alterations with potential to affect offspring phenotype (reviewed in [21]). Nevertheless, in this review, we discuss current evidence supporting a role of the spermatozoal epigenome, in particular DNA methylation, chromatin, and small RNA expression, as a potential carrier of epigenetic inheritance under lifestyle influences.

## 2. DNA METHYLATION IN SPERMATOZOA

DNA methylation controls numerous cell processes including cell differentiation and embryonic development. During embryonic development, DNA methylation participates in the regulation of gene expression, silencing of transposons, and endogenous retroviral sequences, X chromosome inactivation and genomic imprinting [22,23]. Methylation of DNA is under the control of DNA methyltransferases (DNMTs) and enzymes of the demethylation pathway such as Ten-Eleven Translocation (TET), as well as the thymine–DNA–glycosylase (TDG) and the DNA base excision repair (BER) [24,25]. The vast majority of DNA methylation occurs on cytosines in the genomes within

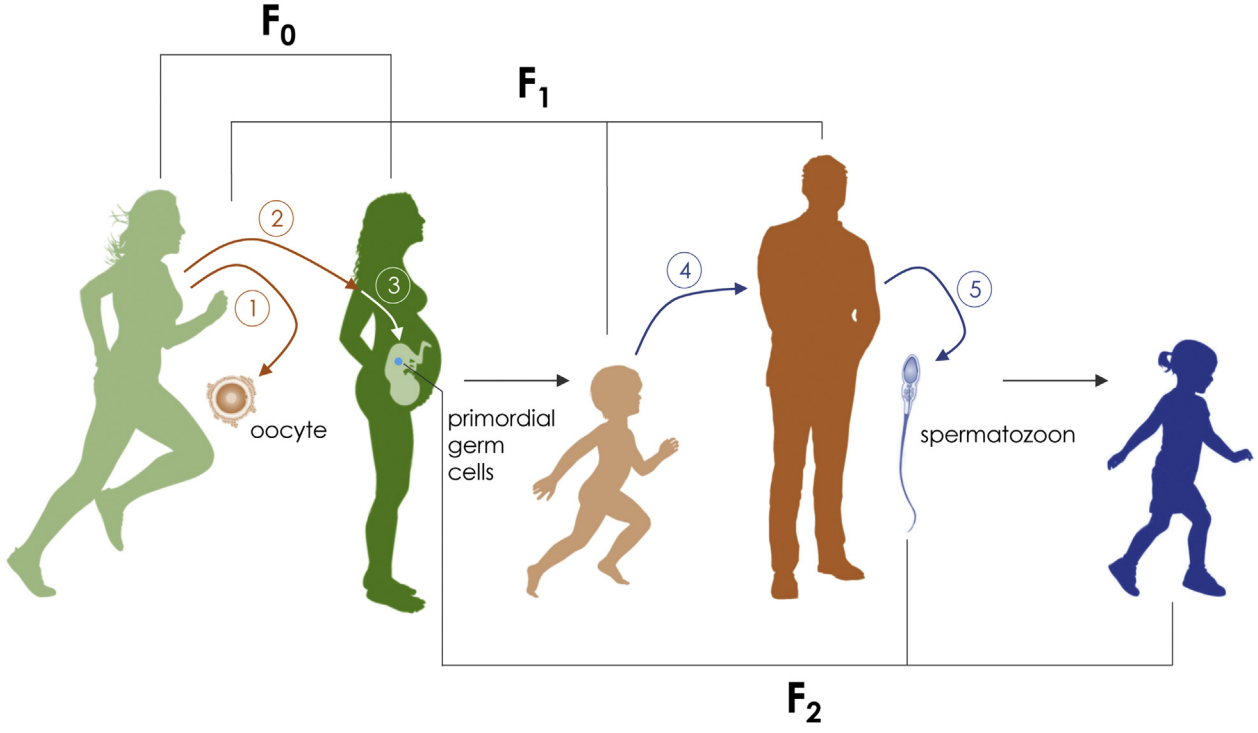


**Figure 1: Lifestyle and environmental influences across generations.** Exercise in the F0 generation may induce epigenetic reprogramming of the oocyte (1), and/or change whole body physiology (2) which, if still persistent when a pregnancy occurs, may have consequences on the extracellular milieu *in utero* (3). The developing embryo could be exposed to the exercise effects, thereby affecting not only the F1 (the embryo itself) but also the primordial germ cells developing in the embryo. Primordial germ cells represent, in part, the second-generation offspring, or F2. Exercise in the F0 may also alter behavior and metabolism in the F1 to influence aerobic capacity or inclination to exercise in the F1, which in turn induces programming of the spermatozoa through serial programming. Alternatively, exercise in the F0 may stably reprogram gametes throughout generations (F0, F1, … ), leading to true transgenerational epigenetic inheritance. Likely, the F2 generation is an integration of all epigenetic reprogramming that occurs throughout ancestors.

 