Gene expression and lifestyles

In recent years, it has become increasingly evident that lifestyles, understood as diet, obesity, working habits, physical activity, and smoking, affect human health. Complex diseases such as cancers, diabetes, and neurodegenerative disorders are due to multiple gene mutations associated with environmental factors; therefore, they depend on close genome–environment interactions. The primary mechanisms by which the environment influences the genome are epigenetic modifications, such as DNA methylation and histone posttranslational regulation (1). Epigenetic modifications, affecting chromatin organization, may regulate the expression of genes encoding proteins, as well as genes producing noncoding RNAs, which, particularly microRNAs (miRNAs), may not only be regulated by epigenetic mechanisms but are also able to control epigenetic mechanisms regulating messenger RNA encoding DNA methylation enzymes (DNMT1, 3a and 3B) and proteins involved in histone modification (1).

It has been demonstrated that epigenome modifications also influence reproductive health. Extensive epigenetic modifications occur during gametogenesis. Sperms and eggs undergo general epigenome remodeling that makes their genomes silent. After fertilization, during early development, the embryo resets parental genomes and reprograms chromatin to give rise to a new individual. In response to environment factors, sperm and egg epigenomes may be modified, and after fertilization these epigenetic changes will affect the developmental programming of the embryo and the health of the unborn child. For example, the offspring of women who are overweight during pregnancy are at increased risk for cognitive deficits, such as attention-deficit/hyperactivity disorder (2). Paternal overnutrition increases body weight and adiposity and impairs glucose tolerance and insulin sensitivity in adult female offspring. Alterations of epigenetic patterns may influence miRNA expression; specifically, let-7 family members have been called diet-responsive sperm RNAs. In fact, different studies indicated that let-7 family members control lipid and glucose metabolisms and are differentially expressed in spermatozoa of the rat fed on a high-fat diet, as well as in the spermatozoa of their offspring (3). Therefore, environmental factors, influencing the gamete epigenome, might cause disorders not only in the offspring but also in later generations.

Another perspective, perhaps less investigated, by which the environment is able to condition reproductive health, is epigenetic modifications in the gonads, which lead to the formation of noncompetent gametes, less suitable for fertilization. Even if it seems to be demonstrated that nonappropriate lifestyles may impair male and female fertility, to date, very few studies have investigated molecular mechanisms that could lead to reduced fertility (4). In this issue of *Fertility and Sterility*, Martinez et al. (5) demonstrate that body mass index (BMI) influences the miRNome of human follicular fluid, and by elaborate statistical analysis the authors find a significant miR-328 up-regulation associated with the increase of BMI. Pathway analysis reveals that the deregulated miRNAs are able to control follicular growth and oocyte maturation. This article represents the first report demonstrating the alteration of biological pathways, inside the ovarian follicle, related to BMI. It could be possible that epigenetic remodeling, attributable to environmental stressors, causes the altered miRNA expression, either directly influencing their transcription or indirectly modulating the expression of protein-coding genes that, in turn, regulate miRNA transcription. Subsequently, miRNA deregulation affects the pathways involved in follicle growth and oocyte maturation. Of course, experimental proof is needed to demonstrate these complex regulation circuits.

The fascinating aspect of epigenetic modifications conditioned by the environment and affecting human health is that, being reversible, it is possible to correct them by changing our lifestyles. Therefore, research aimed at understanding molecular mechanisms by which BMI, diet, working habits, physical activity, or smoking affect human reproductive health is very important and could help to plan nonpharmacologic therapies to improve gamete quality and offspring heath.

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