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Epigenetics in reproductive infertility: A review

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Abstract

Infertility poses a significant challenge to reproductive health worldwide and affects millions of individuals and couples. While genetic factors have traditionally been explored in the etiology of infertility, emerging evidence suggests that epigenetic modifications play a crucial role in reproductive health and infertility. This review delves into the intricate interplay between epigenetics and reproductive infertility, elucidating how epigenetic alterations in germ cells and gametes can impact fertility outcomes. We explore the dynamic nature of epigenetic mechanisms such as DNA methylation and histone modifications, shedding light on their involvement in regulating gene expression essential for proper reproductive function. Understanding the epigenetic basis of reproductive infertility holds promise for developing new diagnostic tools, personalized treatments, and preventive strategies.

Keywords: Epigenetics; Infertility; Fertility; Germ cell

1. Introduction

Since its conceptualization by geneticist and embryologist Conrad H. Waddington in 1942, the term "epigenetics" has evolved to encompass a more comprehensive understanding of the mechanisms underlying gene expression in multicellular organisms. It has been recognized that gene expression is influenced by a combination of epigenetic factors, including DNA modification and histone proteins. Furthermore, over the decades, research has revealed the importance of chromatin modifications in transmitting altered states of activity between cell lineages (1).

Today, epigenetics is understood as the comprehensive study of structural modifications in the genome through DNA and histone marks, which condition the accessibility of transcription factors and inhibit gene expression. These modifications can serve as a kind of cellular memory during embryonic development and morphogenesis and can be perpetuated in cell lineages over time, thus making epigenetics recognized as one of the main causes of infertility (2).

2. Infertility

Infertility, a condition affecting numerous couples worldwide, is a complex issue that encompasses both medical and emotional aspects. It is defined as the inability to conceive a live child and is classified into primary infertility, when a couple achieves a pregnancy that does not result in a live newborn, and secondary infertility, when after a normal pregnancy and birth, they are unable to achieve a subsequent full-term pregnancy with a live newborn.

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The incidence of infertility is significant, affecting approximately nine out of ten couples of reproductive age who have regular sexual relations. It is estimated that between 12% and 20% of couples experience difficulties conceiving, and in recent decades, there has been an increased demand for specialized care in infertility clinics. This increase can be attributed to sociocultural changes, such as the incorporation of women into the workforce, the delay in family formation, the aging population (with a critical factor being the woman's age, as fertility can be affected after 35 years), environmental factors, and of course, epigenetic factors (2).

3. Diagnosis and Treatment

The diagnosis of infertility is essential to identify underlying causes and plan appropriate treatment. An infertility evaluation is recommended for couples who have not conceived after a period of unprotected intercourse, especially for women over 35 years of age or with specific medical conditions. The main causes of infertility include ovulatory dysfunction, tubal diseases, and male factors, although approximately 15% of cases are unexplained.

Lifestyle factors, such as smoking and obesity, can negatively affect fertility, as can ovulatory disorders like polycystic ovary syndrome (PCOS).

Similarly, altered profiles in the expression of non-coding RNA, DNA methylation, and histones have been identified in various cases of infertility, suggesting a significant role of these molecules in its regulation.

It is also important to mention that any alteration in fundamental processes (3) such as oogenesis and spermatogenesis can contribute to infertility itself (4).

To reach a correct diagnosis, all these factors must be considered.

Common treatments include ovulation induction and stimulation, as well as assisted reproductive techniques such as intrauterine insemination (IUI) and in vitro fertilization (IVF). In severe cases, egg or sperm donation may be considered. Additionally, some studies suggest that certain diets may be associated with increased fertility (5).

4. Epigenetic regulation of germ cell development

During the development of testes and ovaries, the specialized cells responsible for producing sperm or eggs (oocytes), known as germ cells, undergo a process called gametogenesis. This intricate process involves the differentiation of germ cells into gametes, such as sperm in males and oocytes in females. Subsequently, the reunion of these gametes through fertilization gives rise to embryos. Throughout gametogenesis and fertilization, there are remarkable changes in cellular differentiation and gene expression. These changes are tightly regulated by epigenetic mechanisms, which govern how genes are turned on or off without altering the underlying DNA sequence. Thus, epigenetic regulation plays a critical role in orchestrating the complex journey from germ cell differentiation to the formation of embryos (6).

In regular cells, epigenetic changes are reversible, enabling the adjustment of gene activity as needed. This process is particularly prevalent in developing germ cells, where epigenetic information is reset. This resetting equips the sperm and egg with the necessary epigenetic instructions to guide embryonic and post-natal development in the offspring (7).

During their migration to the developing gonads, primordial germ cells undergo genome-wide reprogramming, which is a crucial event for re-establishing parent-specific epigenetic information. This is important for organizing sex-specific germ line development and identity. However, epigenetic programming can be susceptible to alteration by various factors. Altered epigenetic states can be transmitted to the next generation and may impact the health and development of offspring, potentially contributing to the developmental origins of health and disease (8).

4.1. Non-coding RNA

As mentioned above, non-coding RNA is a very relevant epigenetic factor in human reproduction. They are functional RNA molecules that regulate gene expression at the post-transcriptional level through epigenetic mechanisms. These RNA molecules have less than 30 nucleotides and can be classified into three main groups called microRNAs (miRNAs), small interfering RNAs (siRNAs) and piwi-interacting RNAs (piRNAs) (9).

miRNAs are estimated to control around 50% of all protein-coding genes and participate in almost all cellular, pathological and developmental processes (10).

The degree of miRNA-mRNA complementarity is considered a key factor in the choice of the post-transcriptional mechanism employed by miRNA (11).

Perfect base pairing results in cleavage of the mRNA and its subsequent degradation, while imperfect base pairing primarily in the 3' untranslated regions (3'UTR) leads to translational repression. siRNAs function similarly to miRNAs and use the same Dicer and RISC complexes to mediate their post-transcriptional gene silencing effect. piRNAs are a more specialized group of short non-coding RNAs and exert their silencing effect by interacting with the P element-induced weak testis (PIWI) family of proteins. piRNAs and PIWI proteins are known to be essential for germ cell development and silencing of repetitive elements such as transposons (12).

4.2. DNA methylation

DNA methylation arises mainly within the framework of guanine and cytosine in the fifth position of the cytosine bases. These dinucleotides are defined as differently methylated regions (also known as DMRs).

Cytosine methylation at DMRs inhibits the process related to the binding of transcription factors to locations that are considered regulatory of relevant genes. In contrast, hypomethylation of regulatory regions is attributed to increased gene expression.

DNA methyltransferases (DNMTs) are called DNMT3A, DNMT1, DNMT3L, and DNMT3B.

One of the enzymes that maintains DNA methylation during DNA replication is DNMT1.

Lack of DNMT1 produces aberrations throughout spermatogenesis.

The enzymes DNMT3B, DNMT3L and DNMT3A participate in DNA methylation during germ cell development in the embryonic phase (13).

Sperm DNA methylation is linked to changes in sperm and infertility. Genes frequently linked to male infertility contain defects related to DNA methylation of mesoderm-specific transcription imprinting genes.

Once the maternal/paternal alleles are demethylated upon fertilization, the genes that are printed retain the methyl marks that belong to the parental genome. Imprinted genes indicate parental-specific activity and are functionally haploid. Therefore, they become vulnerable to epigenetic deregulation.

Rasgrfl, Igf2/H19, Zdbf2 and Dlk¬Gtl2 are paternally methylated genes within spermatozoa H19 gene methylation is related to reactive oxygen species (ROS) levels. H19 DMR methylation levels were found to be lower in infertile men than in fertile men.

According to this, hypermethylation of SNRPN and hypomethylation belonging to the imprinted control region (ICR) H19 are associated with infertility. The risk of this relationship increases with smoking. Furthermore, alcohol consumption is attributed to DNA methylation within regulatory-like regions related to the imprinted gene H19 in human and mouse sperm (14).

4.3. Histones

Histone modifications negatively or positively affect the binding of regulatory factors to DNA, resulting in decreased or enhanced activity.

Acetylation of H3 and H4, methylation of H3K4, and ubiquitination of H2B increase gene expression in testis tissue. In contrast, methylation of H3K27 together with H3K9 and ubiquitination of H2A results in silencing of gene expression (15).

Several histone subtypes, such as H1, H2, H3 and H4 undergo post-translational modifications.

The few human studies on this topic have described an association between altered H3 methylation and poor sperm quality (16).

5. Influence of nutrition on male fertility

Studies have been conducted on how the father's diet can influence the hereditary information found in sperm epigenome. An example of this is folate or vitamin B, which is involved in mechanisms of differential methylation. If there are alterations such as deficiency of this vitamin, analyses indicate an increase in the development of congenital defects and chronic diseases in the offspring (17).

It has also been demonstrated that obesity increases oxidative stress and DNA fragmentation, two factors related to poor reproductive capacity as a consequence of metabolic alterations (17).

High fat consumption has been associated with changes in microRNA expression, which can lead to sperm alterations such as oligoasthenozoospermia. When there are also elevated levels of cholesterol, microRNAs may show a reduction or increase in their expression (18).

Supplementation with specific vitamins (such as vitamin E or vitamin C) and minerals (such as zinc) is associated with an increase in seminal quality and reproductive success (19).

6. Conclusion

Epigenetic changes can significantly influence the fertility of men and women, from sperm quality to ovarian function.

Epigenetic modifications can result from environmental factors such as exposure to toxins, stress, as well as lifestyle factors such as diet and exercise. These changes can alter gene expression in reproductive cells and contribute to fertility problems.

Understanding how epigenetic changes affect fertility may open new doors for diagnosing, treating and developing preventive interventions for infertility.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Jouve de la Barreda N. La epigenética. Sus mecanismos y significado en la regulación génica. Cuad Bioet. 2020; 31(103).

[2] VIDAL C. Esterilidad e infertilidad humanas. FARMACIA PROFESIONAL. 2001.

[3] Sen A, Caiazza F. Oocyte maturation: a story of arrest and release. Front Biosci. 2013; 2(5).

[4] Neto F, Bach P, Najari B, Li P, Goldstein M. Spermatogenesis in humans and its affecting factors. Semin Cell Dev Biol. 2016; 59.

[5] Carson S. Diagnosis and Management of Infertility: A Review. JAMA. 2021; 1(326).

[6] Liu Q, Chen X, Qiao J. Advances in studying human gametogenesis and embryonic development in China. Biol Reprod. 2022; 27(107).

[7] Das L, Parbin S, Pradhan N, Kausar C, Patra S. Epigenetics of reproductive infertility. Front Biosci. 2017; 1(9).

[8] Sun Y, Wang Y, Ge W, Cheng S, Dyce P, Shen W. Epigenetic regulation during the differentiation of stem cells to germ cells. Oncotarget. 2017; 34(8).

[9] Sezgin G, Mehmet AA, Gulgez-Neslihan TH, Ramazan A. The role of epigenetics in idiopathic male infertility. J Assist Reprod Genet. 2016; 33(5).

[10] Kim NV, Ha M. Regulation of microRNA biogenesis. Nat Rev Mol Cell Biol. 2014; 15(8).

[11] Krol J, Loedige I, Filipowicz W. The widespread regulation of microRNA biogenesis, function and decay.. Nat Rev Genet. 2010; 11(9).

[12] Chong WB, Tae-Ki Y, Youngsok C. Functions of PIWI proteins in spermatogenesis. Clin Exp Reprod Med. 2011; 38(2).

[13] Shacfe G, Turko R, Syed HH, Masoud I, Tahmaz Y, Samhan LM, Alkattan K, Shafqat A, Yaqinuddin A. A. DNA Methylation Perspective on Infertility. Genes (Basel). 2023; 12(14).

[14] Erdoğan K K, Sanlier N, Sanlier N. Are epigenetic mechanisms and nutrition effective in male and female infertility? J Nutr Sci. 2023; 12(103).

[15] Skakkebaek N, Rajpert-De Meyts E, Buck Louis G, Toppari J, Andersson A, Eisenberg M, et al. Male Reproductive Disorders and Fertility Trends: Influences of Environment and Genetic Susceptibility. Physiol Rev. 2016; 1(96).

[16] Gunes S, Esteves S. Role of genetics and epigenetics in male infertility. Andrologia. 2021; 1(53).

[17] Xu C, Saint-Phar S, Chountalos G, Gohen T, Paguet M, Suderman M, et al. Low paternal dietary folate alters the mouse sperm epigenome and is associated with negative pregnancy outcomes. Nat commun. 2013; 4(2889).

[18] Oliver-Bonet M, Mach N. Factores nutricionales y no nutricionales pueden afectar la fertilidad masculina mediante mecanismos epigenéticos. Nnitr Hosp. 2016; 5(591).

[19] Eshghifar N, Dehghan B, Do A, Koukgaloo S, Habibi M, Pouresmaeili F. Infertility cell therapy and epigenetic insights. Hum Antibodies. 2021; 29(1): p. 17-26.