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New Frontiers in Research: Reproductive Epigenetics
Review Article

Reproduction and nutriment–nurture crosstalk: epigenetic perspectives

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ABSTRACT

Epigenetics refers to the acquisition and maintenance of heritable states of gene expression that occurs above the level of genetics through alterations in chromatin structure and accessibility. The field of epigenetics has moved much ahead from an emerging science and is growing at a faster pace, as there is increased realization about nutriment and nurture–epigenetic–phenotype relationship. Scientific studies concerning epigenetic changes in the genome in a systematic and genome-wide way provide clinching evidence for epigenetic interactions of environmental and lifestyle factors with genes and determine the reproductive outcomes and health. The epigenetic mechanisms are traditionally studied as DNA methylation, histone modifications, ATP-dependent chromatin remodeling, and noncoding RNA-mediated regulation. In the present review, we have presented an overview of the epigenetics evolved from the interaction and confluence of reproduction and nutrient environment. Besides, our experience with DNA methylation and chromatin modification of the cytochrome P450 aromatase (*CYP19*) gene is also presented. Understanding the emergence of paradigm shift in the reproductive epigenetics appears important as it will open up new vistas for viewing the impact of environment and dietary components on regulation of gene expression concerning the reproductive events and health conditions.

1. Introduction

As we are progressing in the new century, it is also becoming clear that the amazing complexity of regulation at gene level depends on intricate dynamics between various biochemical, physiological, pathological, nutritional, environmental, management, and genetic elements. In the context of regulation of genes, the epigenetic revolution has phenomenal impact in our understanding of modern biology. Today, epigenetics and epigenomics have emerged as one of the gleaming issues and therefore led to the launch of International Human Epigenome Consortium (IHEC) in March 2010 with the primary goal of providing free access to high-resolution reference human epigenome maps for normal and disease cell types to the research community, as well as the discovery of new means to

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treat or manage them. On similar lines, the BLUEPRINT project, aimed at getting the blueprint of hematopoietic epigenomes, was started on October 1, 2011. The events of this epigenetic revolution have definitely affected the researchable areas of mammalian reproduction and at the same time posed challenges to the repro-epigeneticists. Reproduction and epigenetics are mutually inclusive as understood from the cloning experiments, like the 1980s mouse work on 'genomic imprinting', one of the earliest marvels of epigenetics.

In spite of renewed interests and much research in the area of mammalian fertility, infertility, and assisted reproductive technologies (ARTs) during the last decade, the underlying causes and knowledge in many issues and certain basic aspects of reproduction are not yet known or explored. The changes in the ovary are sequential and are dictated by specific, regulated responses to hormones, *viz*., follicle stimulating hormone (*FSH*),[1] luteinizing hormone (*LH*),[2] inhibin,[3] steroids, and growth factors.[4,5] Even the follicular microenvironment[6] has been found to have bigger roles in reproductive events. Some proteases, such as PAPP-A, were implicated in corpus luteum formation and ovarian follicle selection.[7,8] In addition to these mediators for well-coordinated fertility events, it is imperative that epigenetic regulatory machinery may contribute to the fertility. As reported by Richard Lewontin in his classical book of Triple Helix, an organism evolves in a symbiotic relationship along with its genes and environment rather than a simple machine, as stated by Rene Descartes' metaphor, and is undergoing an independent natural selection, like Charles Darwin's theory. Hence, an organism becomes unique even from its twin by its own symbiotic relationship with its genes and environment, which could cause a developmental noise of random cellular events for the uniqueness of an organism. The symbiotic relation not only indicates the effect of environmental or epigenetic factors on the organism, but also the role of an organism to choose an environment for its survival. Therefore, the role of epigenetic factors is not unidirectional to organism but it is bidirectional or mutual.[9] In fact, many epigenetic factors have been identified that have roles in reproduction. There are growing concerns of possible increases in the incidence of genomic imprinting disorders in children born of ART and these could be associated with epigenetic disruption of chromosomal regions or epimutations. Several reports have linked the ART with epigenetically based genomic imprinting disorders, *viz*., Beckwith Wiedemann Syndrome (BWS) and Angelman Syndrome (AS).[10–12] In bovines, one epigenetically based genomic imprinting disorder ''large offspring syndrome'' is evident as it is characterized with an increase in birth weight, polyhydramnios, hydrops fetalis, altered organ growth, and various placental and skeletal defects.[13,14] External factors including environment and food are represented as examples of the nutriment and nurture–epigenetics–phenotype relationship. Lately, there is an increased realization that ''the environment modulates the organism'',[15] and is gradually taking shape as one of the basic tenet of modern biological science.

2. The epigenetic mechanisms

The word Epigenetics (as in ''epigenetic landscape'') was coined by Conrad Waddington (1905–1975) in 1942 as a blend of the words epigenesis and genetics and as equivalent to experimental embryology. It was defined as the branch of biology that studies the causal interactions between genes and their products, and which bring the phenotype into being.[16] Epigenetics was ascribed as a developmental program, where genes determine the individual's phenotype by considering the internal and external environmental cues.[17,18] Epigenetics was also heralded as the study of heritable changes in gene expression that are not caused by changes in the primary DNA sequence.[19] A more appropriate definition of epigenetics is ''the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence''.[20] These changes are effected by several epigenetic mechanisms that include DNA methylation, histone modifications (methylation, acetylation, and phosphorylation), and chromatin remodeling, such as altering the position of nucleosomes, all of which bring about changes in chromatin structure and function. The important role of noncoding RNAs (ncRNA), like miRNA, as an additional epigenetic mechanism in this process, is also being recognized.

2.1. *DNA methylation*

DNA methylation is one of the best-characterized epigenetically mediated transcriptional silencing or repressive events that regulate important cell functions.[21] Majority of imprinted genes in genome happen to be in clusters and sequence elements called imprinting control regions (ICRs) are involved in the regulation of their allele-specific expression. Epigenetic mechanisms, including DNA methylation at ICRs, also known as differentially methylated domains or regions (DMDs, DMRs), control the genomic imprinting. At most ICRs, methylation occurs in the female germline and is inherited from the mother. The most prominent form of epigenetic alteration in mammals is the symmetric methylation of cytosine in the 5′ position in CpG dinucleotides catalyzed by a family of DNA (cytosine-5)-methyltransferases (*DNMTs*)[22,23] that are responsible for the initiation of methylation and maintenance of methylation marks. In 1970s, it was first implicated in the control of gene regulation and X-chromosome inactivation in a heritable manner.[24,25] It also has an important role in the regulation of genomic stability and cellular plasticity. Over a time, DNA methylation was found essential for genomic imprinting, X-chromosome inactivation, and retrotransposons suppression. The genomic imprinting disorders seen in ART were observed with a loss of maternal DNA methylation at imprinted loci, as well as due to the defects in imprinted genes in the sperm of infertile men.[26] It may be plausible to suggest that subfertility and ARTs might interact to predispose newborn to genomic imprinting disorders.[27,28]

During mammalian folliculogenesis, unique epigenetic and transcriptional changes occur in germ cells, including the developing, differentiating, and migrating primordial germ cells (PGCs), growing oogonium, and the developmentally arrested oocytes. In mouse, it was found that global DNA methylation levels are much lower at or around fertilization compared with those that are found in mature gamete and at implantation.[29] The PGCs undergo global epigenetic changes in chromatin organization during and after migration.[30] Here, genome-wide DNA methylation loss appears to initiate in