Chapter

Introductory Chapter: Epigenetics in Summary

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1. Definition

In 1940 the developmental biologist Conrad H. Waddington firstly used the term "epigenetics" to describe "*the interaction of genes with their environment, which bring the phenotype into being*" [1]. Two years later, Conrad Waddington pointed out that "*It is possible that an adaptive response can be fixed without waiting for the occurrence of a mutation*" [2]. Thus, epigenetic modifications are heritable and reversible modifications that significantly affect gene expression without any change in the nucleotide sequence of DNA [3].

2. Molecular mechanisms

Classically, epigenetic mechanisms include (i) the methylation of DNA, (ii) the imprinting, (iii) the remodeling of chromatin, and (iv) the production of noncoding RNA (ncRNA) [4, 5].

The methylation of DNA usually occurs at the 5-position of DNA cytosine (5mC) in the CpG islands located within the promoter region of specific genes; such a modification inhibits both the binding of transcription factors to DNA and affects the recruitment of proteins involved in chromatin remodeling [6, 7], thus causing gene silencing.

Genomic imprinting is a DNA methylation-dependent phenomenon, occurring during embryogenesis; it causes genes to be expressed from a parent of origin-specific manner [8] and specifically interests at some genetic loci.

Nuclear DNA is structured in chromatin, an instructive DNA scaffold that can respond to external cues regulating DNA activity, composed of histone and nonhistone proteins [9]. Euchromatin, which is the transcriptionally active region of the DNA, represents the loosely folded part of the chromatin; heterochromatin, which is a transcriptionally poorly active region of the DNA, represents the tightly folded part of the chromatin [10]. Therefore, the transcription rate of genes is strongly affected by dynamic chromatin remodeling. In this respect, posttranslational modifications of histone tails like methylation and acetylation play critical roles, by affecting either the affinity of transcriptional factors for gene promoter region or the recruitment to chromatin of nonhistone protein, thus disturbing chromatin contacts [10]. Histone tail acetylation usually promotes the transcription and is a feature of euchromatin; by contrast, histone tail methylation has usually an inhibitory role for transcription and is a feature of heterochromatin.

The family of ncRNA includes a large set of RNAs like the well-known microRNA (miRNA) or the less known long noncoding RNA (lnRNA) and tRNA fragments (tRF) among others [11]. NcRNAs are involved in the control of gene expression and in the regulation of many biological functions in several tissues;

their expression rate is affected by environmental cues; thus, their expression rate changes in health and disease. Furthermore, the detection of ncRNA in biological fluids makes them a possible epigenetic biomarker for the prognosis, the diagnosis, and the treatment of diseases [12–14].

Thus, an epigenetic machinery comprising various writers, readers, and erasers that have unique structures, functions, and modes of action like the *de novo* and maintenance DNA methyltransferases, histone acetyltransferases, deacetylases, methyltransferases and demethylases, or the ncRNA biosynthetic pathways has been identified in living organisms [13]. However, additional epigenetic mechanisms such as the delivery among tissues of epigenetic marks within extracellular vesicles, exosomes, or microvesicles are starting to emerge, providing evidence of upcoming communication pathways in which the products of specific cell types may affect the expression rate of specific RNAs in target tissues [15–17].

3. Epigenetics in health and disease

In mammals, epigenetic signature is firstly defined in the embryo [18, 19], but this mark is deeply remodeled during the life course as a direct consequence of environmental cues and lifestyle which includes diet, stress, pollutants, smoking, endocrine-disrupting chemicals, physical activity, sedentary life, etc. Therefore, genome activity is epigenetically modulated under exogenous influence, and the environment-dependent changes in gene activity stably propagate from one generation of cells to the next one. Epigenetic changes impact genome functions, thus affecting health and disease status and also behavior; aging-related diseases, cancer, immunity and related disorders, obesity, metabolic disorders, infertility, and cardiovascular and neurological diseases represent only few examples of environmentally dependent diseases, and the literature in the field is growing up day by day [20–35].

Individual health or disease status strongly depends on epigenetic marks, but "parental experiences" may be epigenetically transmitted to the offspring, thus causing trans-generational epigenetic inheritance and affecting offspring health. Such a process requires the transmission of epigenetic marks through gametes and influences fertilization, embryo development, embryo gene expression, and phenotype [36]. Particularly interesting is the possibility that spermatozoa may use ncRNAs as carrier of paternal experiences, thus providing an "epigenetic memory" capable of affecting embryo development and health with consequences on adult offspring phenotype [13, 32, 33].

4. Conclusions and future perspectives

Taken together, both environment and lifestyle deeply affect DNA functions, and their influence may be transmitted to the next generations with consequences on health status. However, experimental data point out that epigenetic marks, and in particular circulating ncRNAs, may represent upcoming biomarkers for the prevention, the diagnosis, and the treatment of diseases, due to the great potential laying in developing epigenetic therapies [37–39].

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