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 (lncRNA) 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].
Author details

Rosaria Meccariello
Dipartimento di Scienze Motorie e del Benessere, Università di Napoli Parthenope, Napoli, Italy

*Address all correspondence to: rosaria.meccariello@uniparthenope.it

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References

[1] Waddington CH. Organizers and Genes. Cambridge: Cambridge Academic; 1940

[2] Waddington CH. Canalization of development and the inheritance of acquired characters. Nature;150:563-565

[3] Feinberg AP. Phenotypic plasticity and the epigenetics of human disease. Nature. 2007;447:433-440

[4] Kim JK, Samaranayake M, Pradhan S. Epigenetic mechanisms in mammals. Cellular and Molecular Life Sciences. 2009;66(4):596-612

[5] Cholewa-Waclaw J, Bird A, von Schimmelmann M, Schaefer A, Yu H, Song H, et al. The role of epigenetic mechanisms in the regulation of gene expression in the nervous system. The Journal of Neuroscience. 2016;36(45):11427-11434

[6] Holliday R. DNA methylation and epigenetic mechanisms. Cell Biophysics. 1989;15(1-2):15-20

[7] Moore LD, Le T, Fan G. DNA methylation and its basic function. Neuropsychopharmacology. 2013;38:23-38

[8] Ferguson-Smith AC. Genomic imprinting: The emergence of an epigenetic paradigm. Nature Reviews. Genetics. 2011;12(8):565-575

[9] Bannister AJ, Kouzarides T. Regulation of chromatin by histone modifications. Cell Research. 2011;21(3):381-395

[10] Javaid N, Choi N. Acetylation- and methylation-related epigenetic proteins in the context of their targets. Genes (Basel). 2017;8(8):196

[11] Palazzo AF, Eliza S, Lee ES. Non-coding RNA: What is functional and what is junk? Frontiers in Genetics. 2015;6:2

[12] Taft RJ, Pang KC, Mercer TR, Dinger M, Mattick JS. Non-coding RNAs: Regulators of disease. The Journal of Pathology. 2010;220:126-139

[13] Chianese R, Troisi J, Richards S, Scafuro M, Fasano S, Guida M, et al. In reproduction: Epigenetic effects. Current Medicinal Chemistry. 2018;25(6):748-770

[14] Kumar P, Kuscu C, Dutta A. Biogenesis and function of transfer RNA-related fragments (tRFs). Trends in Biochemical Sciences. 2016;41:679-689

[15] Bakhshandeh B, Kamaledin MA, Aalishah KA. Comprehensive review on exosomes and microvesicles as epigenetic factors. Current Stem Cell Research & Therapy. 2017;12(1):31-36

[16] Qian Z, Shen Q, Yang X, Qiu Y, Zhang W. The role of extracellular vesicles: An epigenetic view of the cancer microenvironment. BioMed Research International. 2015;2015:649161

[17] Motti ML, D’Angelo S, Meccariello R. MicroRNAs, cancer and diet: Facts and new exciting perspectives. Current Molecular Pharmacology. 2018;11(2):90-96

[18] Seisenberger S, Peat JR, Hore TA, Santos F, Dean W, Reik W. Reprogramming DNA methylation in the mammalian life cycle: Building and breaking epigenetic barriers. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences. 2013;368:20110330

[19] Hogg K, Western PS. Refurbishing the germline epigenome: Out with the old, in with the new. Seminars
in Cell & Developmental Biology. 2015;45:104-113

[20] Ling C, Rönn T. Epigenetics in human obesity and type 2 diabetes. Cell Metabolism. 2019. pii: S1550-4131(19)30137-8

[21] Renani PG, Taheri F, Rostami D, Farahani N, Abdolkarimi H, Abdollahi E, et al. Involvement of aberrant regulation of epigenetic mechanisms in the pathogenesis of Parkinson’s disease and epigenetic-based therapies. Journal of Cellular Physiology. 2019. DOI: 10.1002/jcp.28622. [Epub ahead of print]

[22] Rutten MGS, Rots MG, Oosterveer MH. Exploiting epigenetics for the treatment of inborn errors of metabolism. Journal of Inherited Metabolic Disease. 2019. DOI: 10.1002/jimd.12093. [Epub ahead of print]

[23] Kato M, Natarajan R. Epigenetics and epigenomics in diabetic kidney disease and metabolic memory. Nature Reviews. Nephrology. 2019. DOI: 10.1038/s41581-019-0135-6. [Epub ahead of print]

[24] Grova N, Schroeder H, Olivier JL, Turner JD. Epigenetic and neurological impairments associated with early life exposure to persistent organic pollutants. International Journal of Genomics. 2019;2019:2085496. DOI: 10.1155/2019/2085496. eCollection 2019

[25] Al-Hasani K, Mathiyalagan P, El-Osta A. Epigenetics, cardiovascular disease, and cellular reprogramming. Journal of Molecular and Cellular Cardiology. 2019;128:129-133

[26] Stylianou E. Epigenetics of chronic inflammatory diseases. Journal of Inflammation Research. 2018;20(12):1-14. DOI: 10.2147/JIR.S129027. eCollection 2019

[27] Richard L, Bennett RL, Licht JD. Targeting epigenetics in cancer. Annual Review of Pharmacology and Toxicology. 2018;58:187-207

[28] Flavahan WA, Gaskell E, Bernstein BE. Epigenetic plasticity and the hallmarks of cancer. Science 2017;357(6348):pii: eaal2380

[29] Landgrave-Gómez J, Mercado-Gómez O, Guevara-Guzmán R. Epigenetic mechanisms in neurological and neurodegenerative diseases. Frontiers in Cellular Neuroscience. 2015;9:58

[30] Sen P, Shah PP, Nativio R, Berger SL. Epigenetic mechanisms and longevity and aging. Cell. 2016;166(4):822-839

[31] Das L, Parbin S, Pradhan N, Kausar C, Patra SK. Epigenetics of reproductive infertility. Frontiers in Bioscience (Scholar Edition). 2017;9:509-535

[32] Stuppia L, Franzago M, Ballerini P, Gatta V, Antonucci I. Epigenetics and male reproduction: The consequences of paternal lifestyle on fertility, embryo development, and children lifetime health. Clinical Epigenetics. 2015;7:120

[33] Jenkins TG, Aston KI, James ER, Carrell DT. Sperm epigenetics in the study of male fertility, offspring health, and potential clinical applications. Systems Biology in Reproductive Medicine. 2017;63(2):69-76

[34] Crews D. Epigenetics and its implications for behavioral neuroendocrinology. Frontiers in Neuroendocrinology. 2008;29(3):344-357

[35] Roth TL. Epigenetic mechanisms in the development of behavior: Advances, challenges, and future promises of a new field. Development and Psychopathology. 2013;25(4 Pt 2):1279-1291

[36] Daxinger L, Whitelaw E. Understanding transgenerational
epigenetic inheritance via the gametes in mammals. Nature Reviews. Genetics. 2012;13(3):153-162

[37] Ahuja N, Sharma AR, Baylin SB. Epigenetic therapeutics: A new weapon in the war against cancer. Annual Review of Medicine. 2016;67:73-89

[38] Valdespino V, Valdespino PM. Potential of epigenetic therapies in the management of solid tumors. Cancer Management and Research. 2015;7:241-251

[39] Mau T, Yung R. Potential of epigenetic therapies in non-cancerous conditions. Frontiers in Genetics. 2014;5:438