Rethinking Orality I

Codification, Transcodification and Transmission of 'Cultural Messages'

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DE GRUYTER

The series is funded with the grant of the Department of Excellence (2018-2022) awarded to the Department of Human Studies of the University of L'Aquila by the Italian Ministry of Education, University and Research (MIUR).

ISBN 978-3-11-071395-4
e-ISBN (PDF) 978-3-11-075198-7
e-ISBN (EPUB) 978-3-11-075206-9
ISSN 2702-7732
DOI https://doi.org/10.1515/9783110751987

Library of Congress Control Number: 2021949681

Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at http://dnb.dnb.de.

Printing and binding: CPI books GmbH, Leck

www.degruyter.com

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Epigenetic Cell Memory

Abstract: The inheritance involves the transmission of DNA sequence and non-genetic information, as epigenetic modifications, across generations, contributing to parent-offspring similarity. Epigenetic inheritance concerns changes in DNA expression, it contributes to the transgenerational transmission of phenotypic variation. In this way phenotypic modifications, that are usually mediated by changes in environmental conditions, can be heritable also from one generation to the next. In the new concept of epigenetic inheritance, epigenetic modifications, which become part of the cellular information cycle, are expressed as a phenotype and are passed on to subsequent generations. This article summarizes the epigenetic inheritance from microorganism to human, highlighting how this process has implications in human health. Moreover, there are reported some known mechanisms that allow to remember the functional adaptation to environmental changes, which consists in the epigenetic memory.

Keywords: Inheritance; epigenetic mechanisms; HDAC; microorganisms; *Candida albicans*; bacteria.

1 Introduction

The state of a biological system is determined by present conditions and by past history. The inheritance involves the transmission of DNA sequence and non-genetic information, as epigenetic modifications, across generations, contributing to parent-offspring similarity. Several evolutionary biologists claim a wider evolution conception. The concept of inclusive inheritance redefines evolution as "the process by which the frequencies of a population's variants change over time" where the word "variants" replaces the word "genes" to include any inherited information, whether genetic or not genetic and with continuous or discontinuous effects.

In addition to genetic inheritance, this theory includes all other inheritance processes such as epigenetic inheritance and cultural inheritance. Both biological and social factors influence the genomic landscape independently and jointly with other forces. Genetic inheritance alone cannot fully explain why we look like our parents. As well as genes, we inherited the environment and culture from our parents, which were partly built by previous generations. Recent evidences

https://doi.org/10.1515/9783110751987-004

suggest that cultural transmission is widespread among animals.[1] Examples concern the influence that cultural heritage has on the choice of mate, on the social structure and on the hunting strategies of predators. Cultural selection is another engine of evolution as it interacts with natural selection in both animals and humans. There are different theories of cultural transmission in humans that diverge in focus and aims. Some authors reported that cultural replication happens when naive learners copy actions. Moreover, Tamariz claims that if actions are not replicated, then culture could not have evolved to produce technology, religion, art, attitudes etc (Tamariz 2019).

All types of inheritance and their complex interactions considerably expand the range of potential evolutionary mechanisms, helping to solve the main evolutionary puzzles (Danchin *et al.* 2011).

Non genetic inheritance of information across generations includes epigenetic changes in DNA expression, which are transmitted to the progeny. Epigenetic modifications are usually mediated by changes in environmental conditions. Genes and environment influence epigenome and phenotype. The phenotype variability which not depends on genetic alterations, is regulated by epigenetic mechanisms. The environment can alter gene expression. The changes in the epigenetic state of a cell is called epigenome.

The epigenome has a memory function in both somatic and germ cells. Parents and children can share the same epigenomic characteristics. The latter is the basis for transgenerational non-genetic inheritance.

The modifications, called epigenetics, are dynamic and quickly change in response to environmental stimuli. Almost every aspect of cellular life is influenced by epigenetics and, therefore, it is one of the most important fields of modern biology.

In this review, the role of epigenetics in the transmission of information is reported.

2 What Is Epigenetics?

"Epigenetic" literally means "in addition to changes in genetic sequence". The term has evolved to include any process that alters gene activity without changing the DNA sequence. The DNA contains all the information that determines the organism characteristics. The DNA contained in a cell of an organism is called genome. It consists of genes which represent the hereditary information of the

1 See Ercolani in this volume, 89 – 103.

cell. In eukaryotic cells, DNA is packaged into chromatin and it is tightly bundled to fit into the nucleus. Chromatin is formed by DNA, proteins called histones, and other proteins present in the cell nucleus. Gene expression is the process by which DNA code is converted into a functional product, that contributes to determine the specific characteristics of the cells. The level of condensation of chromatin varies during the life cycle of the cell and plays a very important role in gene expression. Covalent modifications of histones and DNA can influence the expression of genes. Each cell in an organism contains the same DNA, but the phenotype depends on the way in which the DNA is expressed. In our body, the mature cells, that form different tissues, are morphologically and functionally very different from each other (such as, for example, a neuron and an epithelial cell), even if they all originate from a single cell, the zygote. In a mature cell, only 10 – 20 % of the genes are active, while the rest is inactive. This means that, in different cell types, some genes must be switched on while others must be switched off. Epigenetics is a mechanism for the stable maintenance of gene expression, which allows genotypically identical cells to be phenotypically distinct. Three systems are considered key elements to start and support epigenetic change: DNA methylation; chromatin changes, that include the methylation, acetylation, phosphorylation, ubiquitylation, and SUMOylation of the histone proteins; non-coding RNAs. These systems often work cooperatively, acting together to turn specific genes on or off. DNA methylation is the most studied epigenetic modification. The most abundant methylation in DNA is the addition or removal of a methyl group (CH_3) to the cytosine nucleotide in the regions of DNA where the process of transcription of the gene begins. DNA methylation is mediated by specific proteins called DNA methylase or DNA methyltransferase (abbreviated to DNMT). This epigenetic modification is associated with the transcriptional repression of a gene. DNA methylation, like all epigenetic modifications, is reversible.

However, some DNA methylations are not removed and are inherited in later generations. Like DNA, histones can be modified by adding chemical groups to the amino acids that compose them, in particular in one of their ends (the histone tails). Histone changes are capable of modulating the activation and inactivation of genes. Histone methylation or demethylation are mediated by histone methyltransferases (HMTs). Histone acetylation is catalyzed by histone acetyltransferases (HATs), which transfer an acetyl group from acetyl coenzyme A to the ε-NH^+ group of a Lys residue within a histone. The process is reversible, and the enzymes that catalyze the reversal of histone acetylation are known as histone deacetylases (HDACs).

As other proteins, histones are ubiquitylated through the attachment of a ubiquitin to the ε-NH^+ group of a Lys residue, leading to the degradation of

the protein structure. Phosphorylation of histones H1 and H3 was first observed more than 50 years ago in the context of chromosome condensation during mitosis (Bradbury *et al*. 1973, 131–139). The genome contains numerous non-coding sequences which are transcribed in non-coding RNA. Some of them have been identified as important epigenetic regulators. Animal species express three types of endogenous silencing-inducing small RNAs: microRNAs (miRNAs), endogenous siRNAs (endo-siRNAs), and PIWI-interacting RNAs (piRNAs) (Kim *et al*. 2009, 126–139). The roles of nuclear small RNAs of a broad range of organisms include epigenetic inheritance and developmental gene regulation (Castel 2013, 100).

3 Epigenetics and the Environment

Epigenetic mechanisms are essential to many organism functions. Many epigenetic modifications become biologically stabilized at a particular stage of development and are maintained subsequently throughout the lifetime of the organism. The environmental factors modulate the establishment and maintenance of epigenetic modifications, influencing gene expression and phenotype.

Chemical pollutants, dietary components, temperature changes and other external stresses can indeed have long-lasting effects on development, metabolism and health, sometimes even in subsequent generations. This mechanism is related to the capability of cells to maintain the homeostasis in adverse conditions, modifying metabolism through an alternative genetic expression. Epigenome remodeling by environmental stimuli such as diet, physical activity, hormones or pheromones, affects several aspects of transcription and genomic stability, with important consequences for longevity (Benayoun *et al*. 2015, 593–610).

Diet (Fontana *et al*. 2010, 321–326), exercise (Janssen *et al*. 2013, 23–29), sexual stimuli (Maures *et al*. 2014, 561–544) and circadian rhythms (Orozco-Solis/Sassone-Corsi 2014, 66–72) and others environmental factors can induce epigenetic remodeling. There is a linear relationship between external factors and specific chromatin changes. Data obtained using animal model such as *Drosophila*, *Caenorhabditis elegans*, mouse, rat and also human have demonstrated that parental environmental alterations can affect the phenotypes of offspring through gametic epigenetic alterations. This could explain the prevalence of obesity, type 2 diabetes and other chronic non-genetic diseases in specific population groups (Wei *et al*. 2015, 194–208).

4 Epigenetics and Information Storage

A crucial process in life is the ability of cells to pass useful information to their descendants. Some of this information is encoded within molecules of DNA, including genes that contain specific coded instructions. Another layer of information is epigenetic information, that specify whether individual genes are switched on or off, which means cells with the same genes can perform different tasks (Saxton/Rine 2019, 8).

Several examples demonstrate that epigenetic mechanisms are widely used for the formation and the storage of cellular information in response to environmental signals. The storage of cellular information can be compared to the formation of behavioral memory in the central nervous system.

Some authors propose two different molecular signals of epigenetic states: 'cis' and 'trans' signals. In 'cis memory', epigenetic information is stored in chromatin states that are associated with DNA methylation or histone modifications; in 'trans memory', epigenetic information is stored in the concentration of a diffusible factor such as a transcriptional repressor. A natural system in which is possible to study this issue is the cold-induced epigenetic silencing at *Arabidopsis thaliana* Flowering Locus C (Dean 2017, 140).

5 Epigenetic Inheritance

Environmental signals can induce epigenetic changes that are transmitted to subsequent generations. This phenomenon goes by the name of epigenetic inheritance.

In eukaryotes, chromatin packages organize the genome in order to protect it from environmental insults and to orchestrate all DNA-based processes, including DNA repair and transcription (Allshire/Madhani 2018, 229 – 244). Cells preserve transcription programs and chromatin composition. In this way, chromatin states contain epigenetic information. During cellular replication, the chromatin status is maintained and propagated as cellular identity is one of the key elements in this event. As well as in the somatic cells this can happen also in gametes, guaranteeing the acquisition of epigenetic modifications in the progeny. In the last years, new technologies have permitted many discoveries that have deepened our understanding of transgenerational epigenetic inheritance (Heard/Martienssen 2014, 95 – 109). The specific contribution of individual chromatin components, such as histone post-translational modifications, DNA methylation, or histone variants, is less clear. How the DNA replication and

the cell cycle influence chromatin and the epigenome remains more elusive (Annunziato 2015, 353 – 371). During DNA replication, histone chaperones, epigenetic modifiers and chromatin remodelers accompany the replisome and re-assemble chromatin post-replication. Chromatin components, which carry epigenetic information, are handled at the replication fork determining how nascent chromatin matures post-replication. Advances in technologies are now permitting the analysis of the relationships between DNA replication, chromatin assembly, cell cycle, and epigenome. Nucleosome assembly is tightly integrated with DNA replication. Therefore, chromatin assembly represents a system to study epigenetics, for understanding how chromatin function is inherited in dividing cells and its importance in epigenetic cell memory (Stewart-Morgan *et al*. 2020). An example of inherited epigenetic memory has been demonstrated in *Caenorhabditis elegans*. It has been shown that, in this animal, epigenetic inheritance passes through the production of small non-coding RNA molecules. These small RNAs, produced by natural conditions, are transmitted to the following generations (Greer *et al*. 2011, 365 – 371). An environmental change can induce changes that affect DNA or histones. The modification appears in the germ cell of the adult and is then transmitted to the subsequent offspring through the fertilization process.

Agrawal *et al*. (Agrawal *et al*. 1999, 60 – 63) reported that *Daphnia cucullate*, a tiny crustacean known as "water flea", responds to the chemical signals of its predators by increasing the size of the "helmets", extensions of the exoskeleton that most protect the animal. Its nonexposed progeny born with the enhanced helmet, even in the absence of predator signals. This effect continues in subsequent generations but, in absence of a new signal, the helmet becomes smaller and smaller.

Indeed, the epigenome can change rapidly in response to signals from the environment and in many individuals, multiple epigenetic changes may occur at one time. Through epigenetic inheritance, some of the parental experiences can pass on to future generations. Epigenetic inheritance, therefore, can allow an organism to continuously adjust its gene expression in order to adapt to the environment, without changing its DNA code.

6 Memory and Epigenetic in Bacterial Cells

Phenotypic heterogeneity is common in bacteria and frequent during adaptation to environmental changes. Inheritable phenotypic diversity without DNA sequence changes is controlled by epigenetic mechanisms. In bacteria, the epigenetic mechanisms range from feedback loops to DNA methylation patterns (Ca-

sadesús/Low 2013, 13929 – 13935). DNA-protein interactions, as in eukaryotes, are controlled by DNA methylation, found in bacterial genomes. In many bacterial species, such as *Escherichia coli* and *Salmonella* Typhimurium, methylation controls reversible switching of gene expression, that generates phenotypic cell variants (Sánchez-Romero/Casadesús 2020, 7 – 20). Some authors suggest the presence of a long-retention effect, or "memory effect," of the persister cell state, which is described in the colony-biofilm culture of *Escherichia coli* and a wide variety of other bacteria (Miyaue *et al.* 2018, 1396). The actual extent, variety and potential selective value of prokaryotic memory devices remain open questions, still to be addressed experimentally. Possible implications could interest the role of epigenetic in bacterial resistance and adaptation against immune system and drugs, factors which contribute to determine bacterial pathogenicity.

7 Memory and Epigenetic in Fungal Cells

Chromatin modifying elements have been implicated in fungal morphogenesis and virulence. In *Candida albicans*, biofilm, adhesion and morphological transitions are epigenetically modulated and have been linked, more-or-less specifically, to defined processes.

Epigenetic variations during the infections, such as yeast-hyphae transition, contribute to the fitness of *Candida albicans* in a specific host niche. In this fungal specie there are different epigenetic modulators that regulate the phenotypic transitions (Rotili *et al.* 2009, 272 – 291).

In our previous studies, we have evaluated the inhibition of adhesion, which is the first step of biofilm formation, using histone deacetylases inhibitors. The results demonstrated 90 % reduction in the adherence of *Candida albicans* to the human cultured pneumocytes. Moreover, we have demonstrated that histone deacetylase inhibitors inhibited germination in several strains. The treatment with different histone deacetylase inhibitors resulted in transcriptional down regulation of EFG1 and this is proportional with the ability to inhibit germ tube formation. These histone deacetylase inhibitors were consequently able to affect a step that is considered crucial in giving *Candida albicans* its potential to cause systemic infections *in vivo* (Simonetti *et al.* 2007, 1371 – 1380).

Important issues in fungal infections, which are common in compromised patients, are treatment failures that are associated with the emergence of azole-resistant strains of *Candida albicans* during treatment, in vivo and in vitro. Acquired resistance to azoles and other drugs was shown to be inducible. This antifungal resistance has not been associated with plasmids or other trans-

ferable genetic elements but is thought to involve primarily mutations and genetic or epigenetic rearrangements.

In cultures, histone deacetylases inhibitors have minimal effects on *Candida albicans* growth but, in combination with fluconazole, showed a strong reduction of the resistance induction through regulation of CDR and ERG genes (Mai *et al.* 2007, 1221–1225).

Studying epigenetic mechanisms in fungal pathogens can reveal innovative therapies and treatments which go beyond the resistance equipment that these species have.

Saccharomyces cerevisiae is a well-studied model system for epigenetic regulation and inheritance of chromatin states. This specie has provided a wealth of information on the mechanisms behind the establishment and maintenance of epigenetic states, not only in yeast, but also in higher eukaryotes. In higher eukaryotes the hereditary domains of chromatin are of H3K9 and H3K27 with trimethylation (H3K9me3), (H3K27me3), associated with repressed chromatin. The experiences determine modifications at phenotype and genotype level. Both memory and learning depend on a variety of communicative processes within the whole organism (Witzany 2018, 1–16).

8 Memory and Epigenetic in Mammalian Cells

In addition to genes, we inherited from our parents the environment and culture, which have been partially built by the previous generations.

Non-DNA sequence-based inheritance of information occurs in multiple species and it is important for development and physiology. Several reports on transgenerational responses to environmental or metabolic factors in mice and rats have been published. The inheritance of environmental factors is due to epigenetic modifications as DNA methylation; Wei and colleagues showed that in male mice prediabetes, caused by streptozotocin, affects DNA methylation in sperm, leading to a pathological picture in pancreatic islets of offspring (Wei *et al.* 2015, 194–208).

As said before, different mechanisms can determine the parental effects over a single generation with phenotypic consequences. For example, the progressive loss of function in cells, tissues and organs associated with aging is influenced by both genetic and epigenetic factors. (Carlberg/Molnár 2019).

Epigenetic inheritance of transcriptional repression can be perturbed by environmental insults, with gradual restoration over generations leading to a transgenerational transfer of information about ancestral environmental experience.

In animals, the epigenetic profile of cells sums up the signals that the organism has faced during his life, progressively edifying a kind of cellular memory. Epigenetic modifications record the experiences of cell modifying genic expression. During embryonic development, the organism receives external stimuli which orchestrate tissue differentiation, permitting cells to assume distinct identity and specialized function. In mammals, changes in gene expression, which modify cellular function and properties in response to environmental pressure, are often propagated from mother to daughter cells (Ehrenhofer-Murray 2004, 2335 – 2349; Levenson/Sweatt 2005, 108 – 118).

The study of epigenetics and social epigenomics permits to understand the complex connection between biology and socio-cultural factors such as diet, stress, environment and cancer. In human, different biological, environmental, and socioeconomic conditions may contribute to racial disparities in lung cancer as effect of different epigenetic modifications in pneumocytes.

Terry and colleagues, reported that lung cancer is associated with race of African Americans, which have the DNA more hypomethylated than Non-Hispanic White or Hispanic (Terry *et al.* 2008, 2306 – 2610).

Moreover, social stressors such as stress, starvation, domestic violence and war has been shown to alter methylation status, increasing susceptibility to develop pathologies (Watson *et al.* 2019, 87).

Some authors reported that individual behavioral identity such as diet, physical activity, smoking and alcohol consumption affects the phenotype of the subsequent generations through epigenetic modulation of spermatozoa (Donkin/Barrès 2018, 1 – 11). Epigenetic changes determined by environmental factors persist even after the removal of the inducing agent, causing long-lasting effects.

Obese and lean men have a different epigenome which can be passed on the offspring, affecting subsequent generation's health (Marsit 2015, 71 – 79).

Ahmed reported that traumatized individuals can transmit metabolic modifications until the third generation. This mean that trauma has negative consequences on spermatozoa and ova which are the links between generations (Ahmed/Alsaleh 2019, 115).

Otherwise, favorable environments and healthy behaviors can have positive consequences on the germ cells in individuals and consequently on the offspring.

Some authors showed that dietary percent of macronutrients are correlated with DNA methylation (Williams 2017). The food can influence the epigenetic state of cells, therefore can change gene expression and be inherited from our offspring.

In conclusion, epigenetics has overturned the rules on cell identity, inheritance and disease. It represents a real revolution for biology and offers answers

to problems of general interest, providing new weapons against human affections.

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