Palestrica of the third millennium – Civilization and Sport
Vol. 17, no. 4, October-December 2016, 283–289

REVIEWS

An epigenetic approach of the symbiotic relationship between nutrition and systematic physical activity

O abordare epigenetică a relaţiei simbiotice dintre nutriţie şi activitatea fizică sistematică

Nicolae Neagu
University of Medicine and Pharmacy, Tîrgu Mureş

Abstract

Our study starts from the assumption that the influence of the environment (phenotype) can modify, positively or negatively, genetic heritage, as an epigenetic factor. Recent research reveals several cellular mechanisms by which environmental influences can control gene activity. These mechanisms (epigenetic activity) allow body cells to adapt to environmental changes. We investigated the literature to clarify some terms: epigenetics, genome, epigenome, microbiome, less circulated in our area, as well as the relationship of mutual potentiation between genotype and phenotype as co-variants of motor capacity, body morphotype and homeostasis. From the relation between individual nutrition and the typology of daily activities, we developed several deductions and analogies, considering that a monitored correlation mutually potentiates the influences of the two environmental factors. Our approach raises the problem whether epigenetics could answer the original question if environmental changes in ancestors generate epigenetic changes in their descendants, inducing a new epigenome, better or worse than the previous one.

Key words: epigenetics, genotype, phenotype, genome, microbiome.

Rezumat

Studiul nostru porneşte de la premiza posibilităţii că influenţa mediului ambiental (fenotipul) poate modifica, pozitiv sau negativ, zestrea genetică individuală, ca factor epigenetic. Cercetări recente relevă că există mecanisme celulare, prin care influenţele ambientale pot controla activitatea genelor. Aceste mecanisme, ca activitate epigenetică, dau posibilitatea adaptării celulelor corpului la modificările ambientale. Am investigat literatura de specialitate cu scopul clarificării semantice a unor termeni: epigenetică, genom, epigenom, microbiom, mai rar vehiculaţi în domeniul nostru, respectiv, relaţia de potenţare reciprocă dintre genotip şi fenotip, covariante ale capacităţii motrice, morfotipului somatic şi homeostaziei organismului. Din relaţia dintre caracteristicile dietei individuale şi tipologia activităţilor cotidiene, dezvoltăm deducţii şi analogii, apreciind că o corelare monitorizată potenţează reciproc influenţele celor doi factori ambientali. Abordarea noastră ridică problema dacă epigenetica ar putea răspunde la întrebarea-premiză iniţială şi dacă modificările ambientale longitudinale asupra antecesorilor generează schimbări epigenetice asupra descendenţilor acestora, inducându-le un nou epigenom, superior sau inferior precedentului.

Cuvinte cheie: epigenetică, genotip, fenotip, genom, microbiom.

Introduction

The fact that the entire phylogenetic evolution of the human species was and still is under the influence of two main groups of influence factors is unanimously recognized. These are *internal, endogenous factors and external, exogenous factors*. From another perspective, internal factors are subordinated to the concept of *human genotype*, based on the human species-specific DNA configuration that makes up the *genome* of each individual, while external factors (*human phenotype*) introduce alterations of the human genome organization, without modifying the DNA sequence, generating a particular (individual) form of manifestation, termed *epigenome*.

Consequently, it can be said that the *genome* is a "data library" containing information, the so-called "instruction manual", comprising about 25,000 genes that control everything that happens to an individual (Restian, 2010). On the other hand, the way in which these "instructions" are used, under the considerable influence of the external environment, is a very important interface between the

Received: 2016, November 20; *Accepted for publication:* 2016, December 7;
Address for correspondence: Universitatea de Medicină şi Farmacie Tîrgu Mureş, Str. Gheorghe Marinescu Nr. 38, Tîrgu Mureş, CP 540139, România
E-mail: neagu.nicolae@umftgm.ro
Corresponding author: Nicolae Neagu, neagu.nicolae@umftgm.ro

genome and the environment, inducing a new genomic construct - *ad certum limitatum tempus* - represented by the individual's *epigenome*. In other words, "epigenetic differences between individuals can become heritable across generations" (Ayala & Arp, 2010), with the mention that they are reversible when the specific inducing factors no longer act. It results that epigenetic influence causes changes which:

- induce and support the development and phenotypic variability of the body;
- explain how cell differentiation occurs;
- show that humans are not rigidly genetically determined;
- the genome is a stable component;
- the epigenome is an adaptive component;
- the epigenome updates only those potentialities of the genetic heritage that correspond to current needs.

Regarding these mechanisms, "The epigenome integrates the information encoded in the genome with all the molecular and chemical cues of cellular, extracellular, and environmental origin. Along with the genome, the epigenome instructs the unique gene expression program of each cell type to define its functional identity during development or disease" (Rivera & Ren, 2013, cited by Kanherkar et al., 2014).

The aim of this study is to reveal a number of aspects regarding the way in which the epigenome influences the relationship that we define as *symbiotic* between systematic physical exercise and the characteristics of nutrition in an individual. We do not intend to study in detail the intricate changes in gene organization and restructuring through methylation or other mechanisms – without effective mutations – all induced by epigenetic factors.

In contrast, we wish to analyze some aspects related to the way in which the *genome*, by "reading" epigenetic information, alters a series of characteristics in individuals and their descendants (across two or three generations), under the longitudinal (long lasting) influence – positive or negative – of the environment, such as the quantity and quality of nutrition in relation to the typology of an individual's daily activities, sedentary or active. Possible effects can be defined as either *mutual potentiation* or *mutual disruption*.

Through this study, we wish to draw attention to some increasingly widely spread *mutual disruption* phenomena, which develop insidiously and have a negative influence on the mutual *potentiation* relationship that should be maintained and optimized.

In fact, there are many and varied signs of this true scourge combining a sedentary lifestyle and an unhealthy diet, which has already induced important epigenetic changes that are transmitted to one up to two or three consecutive generations of descendants: infantile obesity, type 2 diabetes mellitus – at increasingly younger ages – cardiovascular diseases, extensive and premature morbidity, a high incidence of mortality due to a deep alteration of the body homeostasis, as a result of a completely inadequate lifestyle including involuntary and paradoxically, voluntary denutrition – tolerated for the "voracious" pleasure of eating without control.

All these are fatefully combined with chronic sedentariness, generated by educational misconceptions and the transformation of daily activities, relating to:

- automation and robotization;
- passive transportation – by car, subway, elevator, escalator, etc.;
- online communication and "pseudo-socialization";
- predominantly electronic games or use of tablets by children;
- insufficient curricular or extra-curricular physical activities;
- early education in the spirit of avoiding effort, followed by the children's refusal to perform physical activities and sports, considered too tiring and straining, etc.

Epigenetics - concept and evolution

Epigenetics emerged as a new science in the early 40's. It was developed by the English biologist

Conrad Hal Waddington (1905-1975). The term *epigenetics* was used for the first time in 1942, in Waddington's book (Waddington, 1942a), *Science and Ethics*. The same year, Waddington (Waddington, 1942b; Waddington, 1942c) published two articles, in which he developed the concept of *epigenetics* following experimental studies related to the influence of environment on the genome. In fact, the pioneer of epigenetics is the German biologist August Weismann (1834-1914), who experimented some environmental influences on the genome in mice. In 1956, Waddington (Waddington, 1956) published a paper in which "he demonstrates the inheritance of some traits acquired by a population, in response to environmental stimuli" (Noble, 2015). Starting from Waddington's new approaches, certain unorthodox formulations are also found, such as: "Epigenetics is a reaction against genetic deficiencies" (Morange, 2005).

Later, in the mid-70's, studies and new approaches of epigenetics developed, which was interpreted as a "control of gene activity, through DNA methylation and alteration of chromatin components" (Morange, 2005).

The epigenetic approaches of Acad. Prof. Dr. Adrian Restian are also interesting. According to him, "Although leading to extraordinary progress, genetics was not able to explain some biological or pathological processes. For example, genetics cannot explain how cell differentiation occurs", from the egg cell to about "200 different types of cells in the body" and "All cells in the human body are derived from the same egg cell and have the same genetic information. All body cells contain the entire genetic information, that is, all have the same genetic potential. However, genetics cannot explain why one cell activates a certain part of genetic information, becoming a neuron, and another cell activates other genetic information, becoming a muscle cell" (Restian, 2010). Adrian Restian also shows that "Genes are normally silent, they only synthesize proteins when they are stimulated by environmental factors, when the synthesis of those proteins is required. And environmental factors act on the genome through the epigenome" (Restian, 2010). Or, "The epigenome is a sort of interface between the environment and the genome" (Leberder, 2001; Bell & Beck, 2010, cited by Restian, 2010).

There are currently many studies that investigate epigenetics, its role, its mechanisms and their transgenerational effects, and transgenerational persistence as new concepts (Paoloni-Giacobino, 2014). A group of researchers at the Washington University demonstrated by personal studies the persistence, across four generations of rats, of epigenetic demethylation phenomena (Anway et al., 2005). At the same time, other pertinent observations show that "generalizations and the temptation to consider epigenetic inheritance as a general rule should be avoided" (Paoloni-Giacobino, 2014). A statistical analysis conducted by *Thomson Reuters Web of Knowledge* regarding the number of studies on epigenetics in the period 1992-2011 evidenced an 850% increase of their number, from about 1000 articles in 1992 to more than 8500 articles in 2011 (Fig. 1).

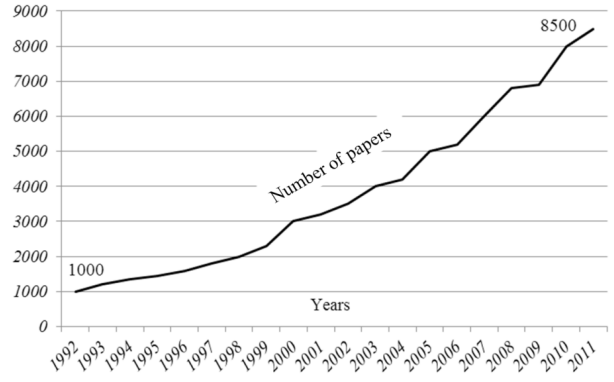

Fig. 1 – Evolution of the number of papers and studies on epigenetics (according to Thomson Reuters Web of Knowledge – Special Topics epigenetics database)

Characteristics of nutrition and its epigenetic impact

A number of studies address the relationship between nutrition as a *sociogenic environmental* factor and its effect on the individual genome, in which it can induce epigenetic changes. The concept of the "first 1000 days of an individual's life" including the prenatal period, and their importance for the epigenetic imprinting of the child's DNA are well known. Relatively recent studies show that inadequate nutrition during pregnancy leads to a marked increase in the rate of non-communicable diseases in offspring (Bedford-Russell & Plumb, 2006; Godfrey et al., 2011; Godfrey et al., 2015; Krushkal et al., 2014). For example, nutritional intake to the fetus through the umbilical cord during pregnancy and in the first months of life has long-term consequences on that individual's health (Godfrey et al., 2015; Tarry-Adkins, 2016).

Lately, the concept of the "first 1000 days" has been extended to a more comprehensive concept, with general applications, the "window of opportunity", which we propose to be included in nutritional guidelines for the mother (with effects on the fetus), and subsequently for the newborn and the child until the age of 3-5 years, which is considered to be the ideal period, with the highest plasticity of the child's development under the influence of environmental factors such as nutrition and physical activity.

The level of an individual's plasticity under external influences decreases with age, which is why a timely phenotypic intervention is important, hence the concept mentioned above. After this optimal period, "the open window" gradually turns into a "closed window against opportunity" or even into a "wall against opportunity", much more difficult to penetrate and influence by environmental factors. Behavioral nutritional or other errors (socioeducational, informational, etc.), translating into nutritional *disorders* or *involuntary denutrition* (through lack of knowledge) and *voluntary denutrition* (out of ignorance), will result in epigenetic marks with long-term negative consequences on the individual's development, as well as on the individual's offspring (Bossdorf et al., 2008).

In various circles interested in the study of epigenetics, with reference to the transmission of genetic predispositions from ancestors to descendants, obesity occupies a central position regarding the interaction between the environment and the individual. *Denutrition* and *sedentariness* are seen as *disturbing obesogenic factors* and the environment becomes an *obesogenic environment*. In such an environment, the epigenetic imprint on the DNA – without changing it (Bird, 2007) – determines a high expression of obesity genes and a low expression of longevity genes. Thus, more than 40 genetic variations have been associated with obesity and adipose tissue distribution (Herrera et al., 2011; Chambers et al., 2008; Lindgren et al., 2009). It was also found, in twins, that the heritability index of the *body mass index* (BMI) in children and adults ranges between 40-70% (Wardle et al., 2008).

Although studies in this area have multiplied, the causal relationship and the covariance relations of the contribution of internal (genetic) and external (environmental) obesogenic factors to what can be defined as *epidemic obesity* are not yet completely understood (Herrera et al., 2011). The same studies show that the specific (more restricted) obesogenic environment has different effects on individuals who live in the same but more extensive environment. Hence certain limitations and hesitations in generalizing one or another hypothesis of obesogenic causality. In fact, this is an extremely wide research area, with many unknown variables, which remain to be discovered and clarified.

Another direction in exploring the study of epigenetics is the development of the concept of *pharmacogenetics*. This involves the discovery of epigenetic drugs, which treat diseases and lead to the inhibition of "disturbing" genes and the activation of "potentiating" genes, offering hope regarding the possibility of "encoding" genes with a triggering role in certain diseases, so that pathogenic genes are silenced (e.g., cancer, morbid obesity, schizophrenia, autism, Alzheimer's disease, type 2 diabetes mellitus, cardiovascular diseases, metabolic disorders and many others). Thus, there is hope that in the future, the DNA will be recoded and adjusted according to the therapeutic and prophylactic needs of tomorrow's society.

Other findings reveal the fact that food acts on the cellular genome through epigenetic factors. In order to be assimilated, food first acts on the cellular genome. The

ingested glucose will initially act on the cellular genome to stimulate the synthesis of insulin and enzymes required for its metabolization. These aspects are investigated by *nutrigenomics,* which studies the influence of nutrition on the cellular genome (Simopoulos, 2002).

Recent studies have shown that inadequate nutrition (high-calorie, high-fat or high-carbohydrate content), smoking and excessive alcohol consumption as environmental factors lead to the development of diseases, acting in turn on epigenetic factors, and that a number of traits can be transmitted across generations through epigenetic factors (Nelson et al., 2010).

Epigenetics, nutrition and the human microbiome

Epigenetic factors, acting on the individual genome, induce changes in gene functions, which impact the different systems of the body. A functional area affected by epigenetic changes is represented by the *individual microbiome* (microbial flora), with long-term effects on the entire digestive activity. The term *microbiome* was introduced by Joshua Lederberg in 2001 (Eisen, 2015). Other relationships, *symbiotic* or, on the contrary, *discordant* can develop auxologically between an individual (as a host) and bacterial and microbial flora (as an epigenetic factor). The result can be positive, ameliorative, optimizing in case of *mutual potentiation* (inducing homeostasis), or obstructive, discordant, antagonistic in case of *mutual disruption* (inducing "dys-stasis") (Fig. 2).

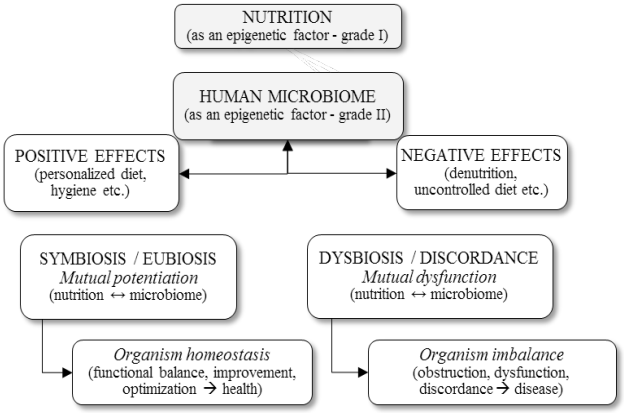

Fig. 2 – Potential influences and relationships between nutrition and the human microbiome, as epigenetic factors.

The human body forms, along with an impressive number of microorganisms - about 100 billion (Kahlert & Müller, 2014), an internal space of cohabitation, generically termed "biozone" or "biocenosis" (biocenosis) – a term introduced by the German biologist Karl August Möbius (1825-1908), in 1877 (Nyhart, 1998). An impressive number of micro-beings "colonize all body-environment interfaces, with genetic information and metabolism, forming the individual human microbiome" (Kahlert & Müller, 2014). In this way, the human body becomes a sort of "superorganism" whose cells "multiply ten times and in terms of genetic information, about 150 times" (Kahlert & Müller, 2014).

The result of this interrelation was defined in 2007 by Eugene Rosenburg and Ilana Zilber-Rosenburg as a *hologenome,* and the theory is termed the *hologenome theory* (Rosenburg et al., 2007; Zilber-Rosenburg et al., 2008). The new resulting functional entity forms a real *holobiosis* between the host organism and its microbiome, and the organism is defined as a *holobiont* (Mustață & Mustață, 2014). Thus, the new gene assembly (host & microorganisms) becomes the *individual hologenome*. The new concept's functioning is based on several rules (Ehrlich et al., 2008; Gilbert et al., 2010):

- Any living organism establishes relationships with internal and environmental microorganisms.
- Microbes are transmitted across generations.
- The interaction between the host organism and microbes influences the interaction of the host with its environment.
- Variations in the individual hologenome are the result of changes in the host genes and microbes (metagenome).

The *microbiome* represents about 2% of an individual's weight. This ratio can be considered low, but through its significant influence on the organism functionality, the microbiome becomes a very important "cohabitant" of the organism. *The microbiome* with its genetic information forms together with the *human genome* an extremely complex *metagenome* (Arumugam et al., 2011).

The colonization of the body by microorganisms occurs progressively. It starts during birth and continues throughout the ontogenic evolution of an individual. In addition to other routes by which this real "army" of microorganisms enter the body (skin, mucosae, respiratory airways, etc.), food is an important "battle tank division" of the microorganism army. Over time, a real "dialogue" takes place between the organism and the microbiome, which has multiple effects, including on the organism's immune system (Salminen, 2005; Stecher & Hardt, 2005; Laparra & Sanz, 2010). This relationship can be *healthy, synchronous* (eubiosis) or *pathogenic, discordant* (dysbiosis) (Fig. 2).

In this context, we mention some recent findings regarding the human organism-microbiome relationship. A group of American researchers at the Washington University found that individuals with a genetic predisposition to obesity have in their intestinal flora bacteria that absorb more nutrients from food. They monitored 12 obese voluntary subjects over a 1-year period, during which these were on a weight loss diet. As the subjects lost weight, the bacterial structure in their intestines changed (Turnbaugh et al., 2006).

The concept of "contagious obesity" has emerged. This means that obesity is not only genetically but also socially transmitted, through an exchange of bacteria between friends and relatives (Christakis & Fowler, 2007; Cohen-Cole & Fletcher, 2008; Bagrowicz et al., 2013).

A recent extensive European project, *MetaHIT* (financed by the European Commission, with a budget of 22 million EURO, implemented in 8 countries in the period 2008-2012), revealed the fact that individuals differ from one another through bacteria in their microbiome (1).

According to recent studies (Arumugam et al., 2011), there are three types of microbial populations, which generate three *human enterotypes,* unrelated to age, sex or diet: *Bacteroides, Prevotella* and *Ruminococcus*.

Bacteroides microbes play a role in carbohydrate breakdown (persons with this enterotype are predisposed to weight problems). *Prevotella* bacteria decompose intestinal mucus, and *Ruminococcus* bacteria enhance sugar absorption, inducing weight gain. Individuals with the *Bacteroides* enterotype have a better synthesis of vitamins B2, B5, C and H, while those with the *Prevotella* enterotype have effective bacteria in synthesizing vitamins B1 and B9 (Slonczewski & Foster; 2011; Rosenburg & Zilber-Rosenburg, 2011) (Fig. 3).

The *Bacteroides* enterotype corresponds to high-fat and high-protein diets, while *Prevotella* is related to a high-carbohydrate diet. As part of the mentioned project, a study in Denmark found that microbiome analysis allows to predict diabetes, the multiplication of *Bacteroides* microbes being more relevant than the *body mass index* (BMI).

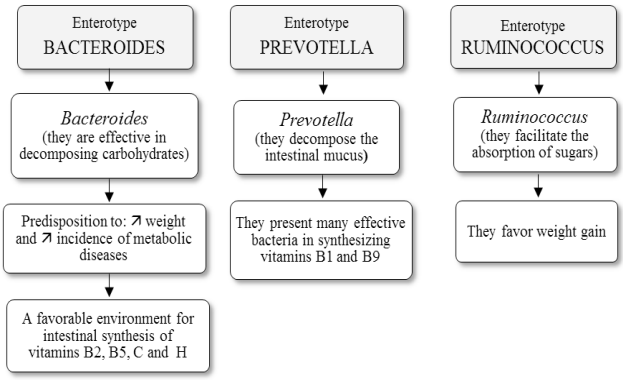

Fig. 3 – The microbiome and human enterotypes (according to the European **MetaHIT** project)

Epigenetics and physical activity

As mentioned before, one of the phenotypic factors that influence the genome and some emerging epigenetic traits is represented by systematic physical activity (longitudinal, in the long term). The positive influences of well conducted personalized physical exercise are known and recognized by most researchers in the field. "Skeptics" are very rarely found when discussing physical exercise based on scientifically verified and validated principles, methods and theories.

We present a number of findings from recent studies in the field of epigenetics.

It was demonstrated that physical exercise performed two times a week for six weeks could alter the methylation of more than 7000 adipose tissues genes (of which 39 involved in obesity and type 2 diabetes mellitus), in a group of 23 middle-aged men, of which 50% had a family history of type 2 diabetes mellitus. Their cells adapted for the benefit of the organism.

Other relevant beneficial effects ($p < 0.05$) were an optimization of individual physical fitness, improved blood pressure and heart rate reactivity during and after exercise, as well as a reduction of cardiovascular risk. The studies were carried out at Lund University, Malmo, Sweden (Rönn et al., 2013).

Other studies show the fact that systematic physical activity has beneficial effects on memory, psychobehavioral balance and impulsivity (Archer et al., 2012; Blum et al., 2015).

Regarding the psyche, the targeted areas are: cognition, affect, personality, behavior, and mental health (Archer, 2015).

One of the many positive effects of systematic physical exercise also acts on the "internal clock", inducing a considerable gap between the biological age and the chronological age of those who are aware of this major benefit. This effect consists of a reversal of the "epigenetic clock" in the aging process (Denham et al., 2013; Lindholm et al., 2015). Physical exercise as an epigenetic factor also contributes to optimizing cardiorespiratory activity and regeneration processes (Zimmer & Bloch, 2015; Kashimoto et al., 2015).

Other studies have demonstrated the fact that systematic physical exercise determines an increase of mitochondrial biogenesis activity in skeletal muscles and an enhancement of biochemical activity during muscle contraction, having beneficial effects on the increase of muscle strength and resistance (Perez-Schindler & Philp, 2015).

Other epigenetic mechanisms influence morphological and functional adaptation in somatic muscles subjected to sustained physical effort. An example is protein *NCoR1* (*nuclear receptor co-repressor* 1), which can reduce the activity of certain genes. Its inhibition induces muscular hypertrophy and an increase in the number of mitochondria, with stimulating effects on physical performance. Potential applications include some positive examples regarding the treatment of myasthenia in the elderly and the development of drugs for obese or immobilized patients, in order to fight physical weakness (Yamamoto, 2011a; Yamamoto, 2011b). However, there are also negative examples, related to the increase, contrary to sports ethics, of muscle strength and resistance in high performance sport (epigenetic doping!!!).

Some studies have evidenced the synergistic relationship between systematic physical exercise and nutrition, as well as the positive effect of personalized diets, which improve various functional disorders, leading to the release of exosomes containing *miRNAs* – non-coding RNA molecules (Tyagi & Joshua, 2014). The Mediterranean diet represents a real benefit for persons with a genetic predisposition to obesity, when it is supported by physical exercise (Ursu et al., 2015). The prerequisites for such positive effects are: longitudinal effort, intensity of effort and frequency of sessions adapted to individual needs and particularities.

Other beneficial effects of the association of exercise with personalized diets have been identified in recent studies: regulation of metabolism, increase of the muscle mass, enhancement of hematopoiesis, and improvement of immunity (Voisin et al., 2015).

Conclusions

Although the area of epigenetics is extremely vast, our study allows us to draw the following conclusions:

1. Epigenetics does not change the DNA and, in addition, we emphasize the idea that epigenetics does not represent an "evolution" in the sense of Darwin's theory.

2. Epigenetic changes are a complex response of the

organism to an external modifying element.

3. The "response" may be inherited and can manifest across generations, through its epigenetic mark.

4. If the epigenetic influence that has generated adaptive changes is removed, the DNA code tends to restore its original program.

5. Environmental factors as epigenetic factors, such as prenatal and postnatal nutrition, stress and the type of activity (physical or sedentary), may leave positive or negative imprints on the generations of descendants, with a higher or lower degree of reversibility, through a reduction or inhibition of the change-inducing actions.

6. Controlled synergism between physical activity and assisted nutrition has many positive effects on the organism, regardless of the individual's status: normal physical fitness, body dysfunction or sports performance.

7. Determining the contribution of endogenous epigenetic factors compared to that of exogenous environmental factors remains an unlimited area to explore, open to further investigations.

Conflicts of interest

Nothing to declare.

Acknowledgments

The study was presented at the National Conference on Sports Nutrition, 2nd Edition, 2-3 November 2016, **Tî**rgu Mureş, Romania. *Organizers*: University of Medicine and Pharmacy Tîrgu Mureş and Romanian Association of Nutrition and Dietetics.

References

Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science. 2005;308(5727):1466-1469. doi:10.4172/2157-7412.1000115.

Archer T, Oscar-Berman M, Blum K, Gold M. Neurogenetics and Epigenetics in Impulsive Behaviour: Impact on Reward Circuitry. J Genet Syndr Gene Ther. 2012;3(3):1000115. DOI:10.4172/2157-7412.1000115.

Archer T. Physical Exercise as an Epigenetic Factor Determining Behavioral Outcomes. Clin Exp Psychol 2015;1(1). http://dx.doi.org/10.4172/2471-2701.1000e101.

Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, Fernandes GR, Tap J, Bruls T, Batto JM, Bertalan M, Borruel N, Casellas F, Fernandez L, Gautier L, Hansen T, Hattori M, Hayashi T, Kleerebezem M, Kurokawa K, Leclerc M, Levenez F, Manichanh C, Nielsen HB, Nielsen T et al. Enterotypes of the human gut microbiome. Nature, 473(7346):174-180. doi:10.1038/nature09944.

Ayala FJ, Arp R. Contemporary Debates in Philosophy of Biology. Blackwell Publishing Ltd. P.127, Wiley-Blackwell, 2010.

Bagrowicz R, Watanabe C, Umezaki M. Is obesity contagious by way of body image? A study on Japanese female students in the United States. J Comm Health. 2013;38(5):834-837. doi: 10.1007/s10900-013-9686-9.

Bedford Russell AR, Plumb J. GBS and the newborn infant. Infant, 2006;2(6):226-227.

Bell CG, Beck S. The epigenomic interface between genome and environment in common disease, Funct Genom. 2010;9(5-6):477-485. doi: 10.1093/bfgp/elq026.

Bird A. Perceptions of epigenetics. Nature, 2007;447(7143):396-398.

Blum K, Braverman E, Waite RL, Archer T, Thanos PK, Badgaiyan R, Febo M, Dushaj K, Li M, Gold MS. Neuroquantum theories of psychiatric genetics: can physical forces induce epigenetic influence on future genomes? Neuro Quantology, 2015;13(1):90-103. DOI:10.14704/nq.2015.13.1.799.

Bossdorf O, Richards CL, Pigliucci M. Epigenetics for ecologists. Ecol Lett, 2008;11:(2):106-115.

Chambers JC, Elliott P, Zabaneh D, Zhang W, Li Y, Froguel P, Balding D, Scott J, Kooner JS. Common genetic variation near MC4R is associated with waist circumference and insulin resistance. Nat Genet. 2008;40(6):716-718. doi: 10.1038/ng.156.

Christakis, NA, Fowler JH. The spread of obesity in a large social network over 32 years. N Engl J Med, 2007;357(4):370-379. doi:10.1056/NEJMsa066082.

Cohen-Cole E, Fletcher JM. Is obesity contagious? Social networks vs. environmental factors in the obesity epidemic. J Health Econ. 2008;27(5):1382-1387. doi: 10.1016/j.jhealeco.2008.04.005.

Denham J, Nelson CP, O'Brien BJ, Nankervis SA, Denniff M, Harvey JT, Marques FZ, Codd V, Zukowska-Szczechowska E, Samani NJ, Tomaszewski M, Charchar FJ. Longer leukocyte telomeres are associated with ultra-endurance exercise independent of cardiovascular risk factors. PLoS One. 2013;8(7):e69377. doi: 10.1371/journal.pone.0069377.

Ehrlich GD, Hiller NL, Hu FZ. What makes pathogens pathogenic. Genome Biology, 2008;9:225. doi:10.1186/gb-2008-9-6-225

Eisen J. What does the term microbiome mean? And where did it come from? A bit of a surprise The Winnower 2015; 2:e142971.16196. DOI: 10.15200/winn.142971.16196.

Gilbert SF, McDonald E, Boyle N, Buttino N, Gyi L, Mai M, Prakash N, Robinson J. Symbiosis as a source of selectable epigenetic variation: taking the heat for the big guy. Philos Trans R Soc Lond B Biol Sci. 2010;365(1540):671-678. DOI: 10.1098/rstb.2009.0245.

Godfrey KM, Costello PM, Lillycrop KA. The developmental environment, epigenetic biomarkers and long-term health. J Dev Orig Health Dis. 2015;6(5):399-406. doi: 10.1017/S204017441500121X.

Godfrey KM, Inskip HM, Hanson MA.The long-term effects of prenatal development on growth and metabolism. Semin Reprod Med. 2011;29(3):257-265. doi: 10.1055/s-0031-1275518.

Herrera BM, Keildson S, Lindgren CM. Genetics and epigenetics of obesity. Maturitas. 2011;69(1):41-49. doi: 10.1016/j.maturitas.2011.02.018.

Kahlert C, Müller P. Microbiome - découverte d'un organe. Forum Med Suisse 2014;14(1617):342-344.

Kanherkar RR, Bhatia-Dey Naina, Csoka AB. Epigenetics a cross the human lifespan. Front Cell Dev Biol. 2014;2(49):1-19. https://doi.org/10.3389/fcell.2014.00049

Kashimoto RK, Toffoli LV, Manfredo MH, Volpini VL, Martins-Pinge MC, Pelosi GG, Gomes MV. Physical exercise affects the epigenetic programming of rat brain and modulates the adaptive response evoked by repeated restraint stress. Behav Brain Res. 2016;296:286-289. doi:10.1016/j.bbr.2015.08.038.

Krushkal J, Murphy LE, Palmer FB, Graff JC, Sutter TR, Mozhui K, Hovinga CA, Thomas F, Park V, Tylavsky FA, Adkins RM. Epigenetic analysis of neurocognitive development at 1 year of age in a community-based pregnancy cohort. Behav Genet. 2014 ;44(2):113-125. doi: 10.1007/s10519-014-9641-2.

Laparra JM, Sanz Y. Interactions of gut microbiota with functional food components and nutraceuticals. Pharmacol Res. 2010;61(3):219-225. doi: 10.1016/j.phrs.2009.11.001.

Epub 2009 Nov 13.
Leberder J. The meaning of epigenetics. The Scientist, 2001;15(18):6.
Lindgren CM, Heid IM, Randall JC, Lamina C, Steinthorsdottir V, Qi L et al. Genome-wide association scan metaanalysis identifies three loci influencing adiposity and fat distribution. PLoS Genet 2009;5(6):e1000508.doi:10.1371/journal.pgen.1000508.
Lindholm ME, Marabita F, Gomez-Cabrero D, Rundqvist H, Ekström TJ et al. An integrative analysis reveals coordinated reprogramming of the epigenome and the transcriptome in human skeletal muscle after training. Epigenetics 2015,9:1557-1569.
Morange M. Quelle place pour l'épigénétique? Medecine/Sciences, 2005;21(4):367-369. DOI: 10.7202/010768ar.
Mustață G, Mustață M. The Microbiome - The Secret Weapon of Modern Medicine. Int. J Med Dent, 2014;4(2):123-137.
Nelson VR, Spiezio SH, Nadeau JH. Transgenerational genetic effects of the paternal Y chromosome on daughters' phenotypes. Epigenomics. 2010;2(4):513-521. doi: 10.2217/epi.10.26.
Noble D. Conrad Waddington and the origin of epigenetics. J Exp Biol, 2015;218:816-818. doi: 10.1242/jeb.120071.
Nyhart Lynn K. Civic and Economic Zoology in Nineteenth-Century Germany: The „Living Communities" of Karl Mobius, Isis: Int Rev devot History Sci Cult Infl, 1998;89(4):605-630.
Paoloni-Giacobino A. Epigénétique et transmission. Rev Med Suisse 2014;10(431):1153.
Perez-Schindler J, Philp A. Regulation of skeletal muscle mitochondrial function by nuclear receptors: implications for health and disease. Clin Sci 2015;129(7):589-599. DOI: 10.1042/CS20150246.
Restian A. Epigenetica. Practica medicală 2010;5(4):237-243.
Rivera, CM, Ren B.. Mapping human epigenomes. Cell J, 2013;155(1):39-55. doi: 10.1016/j.cell.2013.09.011.
Rönn T, Volkov P, Davegårdh C, Dayeh T, Hall E, Olsson AH, Nilsson E, Tornberg Å, Dekker Nitert M, Eriksson KF, Jones HA, Groop L, Ling C. A Six Months Exercise Intervention Influences the Genome-wide DNA Methylation Pattern in Human Adipose Tissue. PLoS Genet, 2013;9(6):e1003572. doi:10.1371/journal.pgen.1003572.
Rosenburg E, Koren O, Reshef L, Efrony R, Zilber-Rosenburg I. The role of microorganisms in coral health, disease and evolution. Nature Rev Microbiol 2007;5(5): 355-362.
Rosenburg E, Zilber-Rosenburg I. Symbiosis and Development: The Hologenome Concept. Birth Defects Research (Part C) 2011;93:56-66.
Salminen SJ, Gueimonde M, Isolauri E. Probiotics That Modify Disease Risk. J Nutr. 2005;135(5):1294-1298.
Simopoulos AP. Genetic variation and dietary response: Nutrigenetics/nutrigenomics. Asia Pacific J Clin Nutritr 2002;11(S6):S117-S128. DOI: 10.1046/j.1440-6047.11.s6.3.
Slonczewski JL, Foster JW. Microbiology: An Evolving Science. WW. Norton & Co New York, 2011.
Stecher B, Hardt WD. The role of microbiota in infectious disease. Trends Microbiol. 2008; 16(3):107-114. doi: 10.1016/j.tim.2007.12.008.
Tarry-Adkins JL, Fernandez-Twinn DS, Chen JH et al. Poor maternal nutrition and accelerated postnatal growth induces an accelerated aging phenotype and oxidative stress in skeletal muscle of male rats. Dis Models Mech 2016;9(10):1221-1229. doi:10.1242/dmm.026591
Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 2006;444(7122):1027-1031. doi:10.1038/nature05414.
Tyagi SC, Joshua IG. Exercise and nutrition in myocardial matrix metabolism, remodeling, regeneration, epigenetics, microcirculation, and muscle. Can J Physiol Pharmacol. 2014;92(7):521-523. doi: 10.1139/cjpp-2014-0197.
Ursu RI, Badiu C, Cucu N, Ursu GF, Craciunescu I et al. The study of the rs9939609 FTO gene polymorphism in association with obesity and the management of obesity in a Romanian cohort. J Med Life 2015;8(2):232-238.
Voisin S, Eynon N, Yan X, Bishop DJ. Exercise training and DNA methylation in humans. Acta Physiol (Oxf) 2015;213(1):39-59. doi: 10.1111/apha.12414.
Waddington CH. Canalization of development and the inheritance of acquired characters. Nature 1942b; 150(3811):563-565. DOI: 10.1038/150563a0.
Waddington CH. Science and Ethics. George Allen & Unwin, London, 1942a.
Waddington CH. The epigenotype. 1942c. Int J Epidemiol. 2012;41(1):10-13. doi: 10.1093/ije/dyr184.
Waddington CH. The genetic assimilation of the bithorax phenotype. Evolution 1956;10(1):1-13. doi:10.2307/2406091.
Wardle J, Carnell S, Haworth CM, Plomin R. Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. Am J Clin Nutr. 2008;87(2):398-404.
Yamamoto H, Itoh N, Kawano S, Yatsukawa Y, Momose T, Makio T, Matsunaga M, Yokota M, Esaki M, Shodai T, Kohda D, Hobbs AE, Jensen RE, Endo T. Dual role of the receptor Tom20 in specificity and efficiency of protein import into mitochondria. Proc Natl Acad Sci U S A. 2011a;108(1):91-96. doi: 10.1073/pnas.1014918108.
Yamamoto H, Williams EG, Mouchiroud L, Cantó C, Fan W, Downes M, Héligon C, Barish GD, Desvergne B, Evans RM, Schoonjans K, Auwerx J. NCoR1 is a conserved physiological modulator of muscle mass and oxidative function. Cell. 2011b;147(4):827-839. doi: 10.1016/j.cell.2011.10.017.
Zilber-Rosenburg I, Rosenburg E. Role of microorganisms in the evolution of animals and plants: the hologenome theory of evolution. Fed Eur Microbiol Soc. Microbiol Rev. 2008;32(5):723-735. doi: 10.1111/j.1574-6976.2008.00123.x.
Zimmer P, Bloch W. Physical exercise and epigenetic adaptations of the cardiovascular system. Herz. 2015;40(3):353-360. doi: 10.1007/s00059-015-4213-7.

Websites
(1) http://www.metahit.eu/ Accessed on 28 October 2016.