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Epigenomic programing: a future way to health?

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It is now generally accepted that the 'central genome dogma' (i.e. a causal chain going from DNA to RNA to proteins and downstream to biological functions) should be replaced by the 'fluid genome dogma', that is, complex feed-forward and feed-back cycles that interconnect organism and environment by epigenomic programing – and reprograming – throughout life and at all levels, sometimes also down the generations. The epigenomic programing is the net sum of interactions derived from own metabolism and microbiota as well as external factors such as diet, pharmaceuticals, environmental compounds, and so on. It is a growing body of results indicating that many chronic metabolic and degenerative disorders and diseases – often called 'civilization diseases' – are initiated and/or influenced upon by non-optimal epigenomic programing, often taking place early in life. In this context, the first 1,000 days of life – from conception into early infancy – is often called the most important period of life. The following sections present some major mechanisms for epigenomic programing as well as some factors assumed to be of importance. The need for more information about own genome and metagenome, as well as a substantial lack of adequate information regarding dietary and environmental databases are also commented upon. However, the mere fact that we can influence epigenomic health programing opens up the way for prophylactic and therapeutic interventions. The authors underline the importance of creating a 'Human Gut Microbiota and Epigenomic Platform' in order to facilitate interdisciplinary collaborations among scientists and clinicians engaged in host microbial ecology, nutrition, metagenomics, epigenomics and metabolomics as well as in disease epidemiology, prevention and treatment.

Keywords: *epigenomic programing*; *gut microbiota*; *mitochondria*; *energy metabolism*; *food and microbial bioactive molecules*; *feces conservation*

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In the decades after Watson and Crick in 1953 had published their article about the structure of DNA (1), it was a generally accepted axiom that biologically important information could only flow from DNA through RNA to proteins and virtually nothing could be added from the outside. However, in the last few years of the last century, a growing body of results indicated an 'intricate crosstalk between the organism and its environment at all levels, with feed-forward and feed-back cycles in the epigenetic and metabolic network of molecular interactions that mark and change genes as the organism goes about its business of living, with effects reverberating and amplified down the generations' (2). These events can be summarized in a statement that all organisms have a 'fluid genome', thus making truth to the statement 'panta rhei', that is, everything floats, by Heraklitos around 2,500 years ago.

In the 1990s, it became evident that prokaryotes play important roles in shaping the fluid genome in eukaryotes (3, 4). Today, a human being is often described as a 'superorganism', consisting of a consortium of vast number of representatives of Viruses, Eukarya, Bacteria, and Achaea. In terms of cell number, adult humans are more prokaryotic than eukaryotic with 90% of our cells estimated to be of microbial, and only 10% of human origin (5). Adding bacteriophages to the number, human cells may account for less than one per mille.

To receive the fullest information regarding this superorganism's behavior in various environment conditions, a set-up of 'omic' technologies have been introduced into medico-biological science and practice:

> *genomics and metagenomics* which analyses the human genome and microbiome structure;

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epigenomics and metaepigenomics, describing how certain genes in eukaryotic and prokaryotic cells are turned on or off without alterations in the DNA nucleotide sequence;
transcriptomics, which measures mRNA transcript levels;
proteomics, which evaluates protein abundance and spectrum;
metabolomics, which determines abundance of low molecular weight cellular metabolites that enable quantitative monitoring of the multiple of various biological molecules and their interactions in the human body;
phenomics that both qualitatively and quantitatively measures organism phenomic changes in response to genetic and epigenetic changes caused by various environmental factors and agents. (6–8)

The multi-'omics' approach is a powerful tool for understanding the functional symbiotic interplay of human eukaryotic and prokaryotic cells and dynamics of molecular modifications of this multi-cellular system in different environmental conditions. Accumulation of 'omic' databases, especially integrated, and their bioinformatic analysis permits a better understanding of the molecular bases of human health and diseases and designing of novel effective drugs and functional foods (8–13).

Analysis of current scientific and clinical data facilitates selection of some molecular and cellular hallmarks (genomic instability, epigenetic alterations, disorders of multiple signal pathways outside membrane and inside cells, water–salt imbalance, disorders of energy metabolism and mitochondrial dysfunction, oxidative stress and imbalance of antioxidative protective mechanisms, accelerated cellular senescence, disorders of proliferation and apoptotic processes, stem cell exhaustion, chronic inflammation, gut microbiota imbalance, altered intra- and inter-species communication in eukaryotic and prokaryotic cells, etc.) that are closely connected with accumulated cellular damages, uncontrolled cellular growth, progressive disorders of neuro-physiological homeostasis, impairments of functional and/or behavioral reactions arising during long-time alterations of a superorganism homeostasis.

When determined, most of these hallmarks are found to be altered in the majority of 'civilization diseases' (atherosclerosis, cancer, obesity, neurodegenerative diseases, type II diabetes, behavioral alterations as autism spectrum disorders). Taken together, these diseases can be looked upon as different manifestations of the same underlying pathophysiological processes. The relative 'balance' between these processes determines the phenotypic expression of corresponding disorder or disease (14–17).

Epigenomics and its link with energy metabolism

In the past decade, the results of many studies have placed epigenomics at the 'epicenter' of modern medicine because it helps explaining the relationship between individual genetic background, aging, lifestyle and environment, and because any perturbations in the epigenotype may result in health disturbances. Epigenomic processes regulate when and how certain genes are turned on or off without alterations in the DNA nucleotide sequence. Epigenetics is the sum of molecular–biochemical mechanisms that focuses on processes regulating the covalent attachment of different chemical groups to DNA, chromatin, histones, and other associated proteins during post-translation period. Epigenetic DNA and chromatin alterations may persist from one cell division to the next and can occur for several cell generations.

In addition to DNA methylation, it is known multiple different classes of post-translation modification of the core histones (e.g. methylation, acetylation, biotinylation, phosphorylation, ADP-ribosylation, ubiquitination, sumoylation), participating in the nucleosome and chromatin structure formation directed to the unfolding of the genetic program for organism development. It has also been shown that the same and other (e.g. glycosylation, glucuronidation, sulfatation) reactions can occur with proteins that do not connect with chromatin (8, 18–23).

Modifications of structural gene activity may be connected with non-coding microRNAs (miRNAs) as well. MiRNAs occur in two variants: small and long. Small miRNAs are 16–29 nucleotide-long eukaryotic and prokaryotic non-coding RNAs that can regulate gene expression on the different post-transcriptional levels by acting as inhibitors of transcription, modulators of DNA and histone methylation, chromatin reconstruction, and so on. Long non-coding RNAS (LncRNAs) are mostly eukaryotic RNA molecules greater than 200 nucleotides. They are regulators of epigenetic silences, transcriptional regulation, RNA processing and modification, and many other cellular functions (24). Currently, about 5,000 mammalian miRNAs have been identified and about 30% of protein-coding genes may be regulated by miRNA (25). Human miRNA, 6–27%, could be detected in the human mitochondria (26). More than half of known prokaryotic cell RNA can also be referred to as miRNAs (10) that can modulate host gene expression (11). On an individual level, epigenomic programing can be tissue- and stage-of-life-dependent, but it may vary markedly between individuals and species (27).

Epigenetics help to explain the relationship between individual genotype and the environment during all stages of life. Perturbations in epigenetic mechanisms may result in various health disturbances (metabolic syndrome, type II diabetes, autoimmune diseases, cancer, autism and so on) and also in phenotypic differences between monozygotic twins (22). Details of biochemical events associated with epigenomic regulations of gene expression in eukaryotic and prokaryotic organisms have

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been presented in some recent papers and reviews (8, 19, 21, 28–35).

Epigenomic DNA and chromatin remodeling are closely linked with processes of energy production and with the levels of total caloric intake in eukaryotic and prokaryotic cells in a superorganism. Mitochondria, besides the production of energy and increased oxygen species, have several biochemical mechanisms by which they participate in epigenetic modification of the nuclear genome, alteration of DNA methylation, chromatin remodeling, formation and microRNA expression (32, 36–38).

It is well known that prokaryote and eukaryote cells share common pathways for energy production, especially in the Krebs cycle (39, 40). It means that in mammalian organisms, mitochondria and human microbiota should consider to be both a collective metabolically active internal 'organ' affecting the host's energy metabolism (39–41) and a regulator of gene expression of the mitochondrial and nuclear genome (18, 36, 38). Cell energy metabolism needs many tens of different enzyme cofactors: vitamins (B_1, B_2, pantothenic acid – B_5, B_6, biotin – B_7, B_9, B_{12}, C, phyloquinone-K1, menaquinone-K2), non-vitamins (NAD, NADH, NADP+, NADPH), adenosine triphosphate (ATF), cytidine triphosphate (CTP), *S*-adenosyl methionine (SAM), 3′phosphoadenosine-5′-phosphosulfate (PAPS), glutathione (GSH), Coenzyme B, Coenzyme M, Cofactor F-430, Coenzyme Q10, haem, alpha lipoic acid, methanofuran, molybdopterin/molybdenum cofactor, pyrroloquinoline quinone (PQQ), tetrahydrobiopterin (THB/BH4), tetrahydromethanopterin (THMPT/H4MPT), minerals (Ca, Cu, Fe^{++}, Fe^{+++}, Mg, Mn, Mo, Ni, Se, Zn), amino acids (arginine, lysine, methionine, cysteine, β-alanine, serine, threonine, histidine, tryptophan, aspartic acid), Krebs cycle organic acids and some nucleotides (pyrimidine), miRNA (26, 36, 39, 42, 43).

Molecular investigations of epigenomic-associated processes have demonstrated (8, 18, 30, 42, 44–46) that most major participants in the epigenomic machinery (Table 1) are formed during energy metabolism in the eukaryotic cell mitochondria and in the prokaryotic cell membranes.

Based on the data presented above, it should be considered that mitochondrial dysfunctions and disorders in energy metabolism in symbiotic prokaryotic organisms may be very important factors predisposing to a wide spectrum of metabolic dysfunctions associated with human epigenome alterations.

Epigenomic programing

Developing organisms appear to be particularly susceptible to epigenetic changes. During very early embryogenesis, the mammalian genome is 'cleaned' of most epigenetic marks, and then a process of 'epigenetic programing' (and reprograming) starts building up individual phenotypes (27, 47). These processes are influenced by many kinds of endogenous and exogenous factors *in utero* as well as later in life (27, 30, 47–54).

Table 1. Main participants and potential inductors of host epigenomic alterations

Main donors of target affect groups or substances	
S-Adenosyl methionine	Methyl group
Acetyl-CoA	Acetyl group
Nicotinamide adenine dinucleotide (NAD +)	ADP ribosyl group
Adenosine triphospate (ATP)	Phosphate group
Coenzyme Q	Ubiquinone
Biotin	Biotin
Nucleotides, double- or single-stranded RNA	microRNA
Some enzymes involved in epigenomic machines	
DNA & RNA and histone methyltransferases; demethylases; acetyltransferases, deacetylases; ribosyltransferases, hydrolases; phosphotransferases, kinases; Bir A ligase; synthetases, nucleases, DNA & RNA-ligases	

Epigenomic programing of cell genome and post-translation modification of gene products are essential mechanisms in the development and postnatal life of higher eukaryotic organisms (gene expression regulation, silencing repetitive DNA elements, cell proliferation, cellular stress events, aging and DNA repair, lifelong circadian drifts, equilibrium between mitosis and apoptosis, modification of bacterial and host cell quorum sensing, host/bacteria crosstalk) (8, 54). Similar programing also takes place in prokaryotes (gene regulation, virulence of pathogens, timing of DNA replication, repair of DNA, phase variation) (18).

Epigenetic developmental plasticity allows an organism to adapt to environmental signals, especially during early life; thereby increasing its own 'fitness'. However, it can also increase the risk of chronic, especially metabolic, diseases. Epigenetic alterations of fetus chromatin and histones might be inherited and affect the health of future generations. There are various combinations of disease-linked DNA, microRNA and chromatin and histone modifications that differ according to chronic metabolic disease type (28, 51, 54).

Important players in the epigenomic programing

Foods and gut microbiota are the two most important environmental factors playing imperative roles in epigenomic programing, and are most pronounced in pregnancy and early in life (8, 18, 28–30, 48, 49).

Foodstuffs, besides water, contain plenty of various macro- and micronutrients. In different GI compartments, these components may be acted upon by host- and microbiota-derived factors (e.g. enzymes, lectins). Depending on physical conditions (pH, redox potential,

oxygen tension) and the microbiota presented in the various compartments, a long set of new compounds may be formed (55). In addition, very rapid diet–microbiota cross-talks are established (56). Both primary and secondary compounds might either be absorbed or excreted in feces. When absorbed, many of them may interfere with epigenomic programing as well as have a more direct nutritional value. An age-dependent demand for many micronutrients is well known; similarly, there seems to be an age-dependent 'window' for epigenomic programing (57).

The list of compounds that might be present in the GI tract is extremely long and includes protein; peptides, including defensins, amino acids, nucleosides, nucleotides, nucleic acids; oligo-, di-, and mono-saccharides; lipopolysaccharides; glycosphingolipids; short chain fatty acids; other fatty and organic acids; bile acids; cholesterol and cholesterol derivatives, including coprostanol, sterols; steroid and other hormones; bilirubins; urobilins; glycans; alcohols; isoprenoides; vitamins; lectins; biosurfactants; antimicrobials; growth factors; oxidants/antioxidants; amines; polyamines (e.g. spermine, spermidines); and gases (CH_4, CO_2, CO, H_2S, H_2O_2, NH_3, NO_3, NO_2, NO) (14, 27, 58).

The 'building stones' for all these molecules are primary externally – especially dietary – derived. It makes sense to have an adequately functioning GI microbiota capable of supplying the host with compounds neither primarily present in the diet nor produced by the host itself. A diet supplying the host, as well as its microbiota, with building blocks is of vital importance. In this context, it has to be underlined that each period of life, from birth to the grave, in pregnancy, and so on, has its own specific dietary requirement (18, 30, 31, 42, 59–64).

Some of the most investigated bio-actives of food and microbial origin capable of interfering with the epigenomic processes are listed in Table 2.

Nutri- and microbial-epigenetics, as a trend in general epigenetics, have appeared quite recently (18, 54, 65, 66). From a functional point of view, bioactive molecules of microbe or food origin may be divided into several groups: metabolic precursors or cofactors, bioactive compounds, pure signaling molecules, metabolic products and molecules possessing simultaneously metabolic and signaling activity. Their effects might be expressed on different host levels: molecular, inside of cell, intercellular matrix, organs and physiological systems. They are able to switch on/off corresponding genes via direct interaction with specific DNA, RNA, or chromatin receptors or using various kinases or other epigenomic-associated pathways.

The following example may reflect the complexity: food- or microbial-derived folate, choline, betain and/or vitamin B_{12} contribute to generating 6-methyltetrahydrofolate which provides the methyl group for synthesis of SAM, the universal methyl donor of epigenomic methylation of DNA and histone proteins. SAM can be converted to *S*-adenosylhomocystein which binds with the methyltransferases and induces product inhibition. Dietary derived epigallocatechin-3 gallate and genistin are able to interfere with the methylation capacity (21). Using rats carrying *agouti* gene as a model (its expression is responsible for a characteristic pattern of banded pigment in individual hair), it has been demonstrated that by changing the amounts of vitamins (B_2, B_6), choline, betain, selenium, and other specific nutrients in the foods of pregnant animals, it is possible to receive posterity with various phenotypic characteristics (color of hair, obesity, or cancer risk). These changes were associated with increasing methylation of CpG islands in the chromosomal DNA (48, 60, 67). It indicates that the acquisition or loss of corresponding epigenomic marks in the host metaepigenome may be the result of surplus or limited availability of the universal donors of methyl-, acetyl-, ADP-, ribosyl-, phosphate groups, ubiquinone, biotin and/or altered expression or activity of corresponding enzymes and their cofactors.

Table 2. Some bioactive components of food and/or microbial origin affecting epigenetic processes

Pectins, oligosaccharides, β-glucans
B1, B2, B6, B12, C, E, D-3, biotin, folic, pantothenic, nicotinic, orotic acids, choline, betaine
Selenium, magnesium, potassium, zinc, iodine, cobalt, iron, iodine, calcium, manganese, copper
Pyruvate, citrate, lactate, α-ketoglutarate, succinate, butyrate, propionate
Arginine, lysine, methionine, cysteine, β-alanine, serine, threonine, histidine, tryptophan, aspartic acid
Adenine, cytosine, guanine
S-Adenosyl methionine, acetyl-CoA, ATP, nicotinamide adenine dinucleotide (NAD +), Coenzyme Q10
Epigenomic process inhibitors or activators (e.g. resveratrol, lycopene, α-lipoic acid)

A shortage of many micronutrients in the current human diet is a global problem. In Table 3, data regarding minerals and also similar shortages found regarding many other compounds is presented (14, 58, 68, 69).

Epigenetic alterations associated with imbalance of diet and symbiotic gut microbiota might be inherited and affect the health of future generations. It is now apparent that food nutrients and bioactive compounds of host microbiota origin play the critical roles in a person's life during a narrow window of time, that is, the 1,000 days beginning at conception and continuing through the second year of life (18, 30, 70–74). During this period, an imbalance in food and/or microbiota may give rise to 'developmental shadows' later in life, as indicated in some of the following examples. Recent results indicate that

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Table 3. The most distributed deficiencies of essential minerals in the human diet

	The necessary amount of microelements (mg/daily)	Number of people (billions) with microelement deficiency	Microelements quantity (mg/kg) in the gut microbe biomass
Zinc	30.0	4.5	499.6 ± 54.4
Copper	2.0	3.6–3.8	46.9 ± 4.4
Chrome	0.15	3	1.44 ± 0.15
Iron	20.0	1	584.9 ± 120.2
Iodine	0.15	1	2.8 ± 0.43
Selenium	0.1	1	1.73 + 0.17

underfeeding or overeating in pregnant women and infants (30), their long feeding with fat enriched foods (22, 23, 30, 75), feeding infant and children with protein deficit diet (23, 30, 76), as well as a diet with certain nutrient deficiencies (22, 30) or chronic alcohol consumption (22) have a negative impact on the epigenomic program of development resulting in general or local specific epigenomic disorders, thereby influencing gene expression and the risk of metabolic imbalance later in life.

On the contrary, food for mothers and infants containing enough compounds for an adequate epigenomic programing are assumed to be of importance for health later in life (18, 27, 77–81). However, as underlined by Park et al. (77), in this field, 'there is much to be done that has great potential to yield findings with significant public health implication'.

Where do we go from here?

Accepting the fluid genome axiom, the growing body of data indicating that many metabolic 'civilization diseases' are due to epigenomic programing disorders, especially in a certain period after fertilization, and also many data indicating that we can influence upon this programing, represent a huge challenge to human society. The tasks ahead of us can very briefly be summarized as follows.

Genome characterization – either *in utero* or at birth – is here to stay. In the context for prevention of civilization diseases, this knowledge is still of very limited value. However, when we have more information about epigenetically 'sensitive' regions as well as external and internal factors capable of 'playing' on these regions in an age-dependent matter, it is easy to forecast that an individual genome characterization will increase in importance.

Microbiome characterization. This approach is also here to stay. However, we do have to accept that even the largest investigations represent 'fecal snap-shots' (e.g. one or few fecal samples taken over a short period of time in a limited number of individuals). Most of the results published so far are from individuals living on food based on a few carbohydrates (wheat, rice, corn, and potatoes). The need for studies in larger groups of individuals followed over longer periods of time is obvious, as well as the need for data from cohorts living on other sources of carbohydrates (82, 83); more information is also needed about microbiota in various intestinal compartments. In addition, accepting the lifelong cross-talks that take place between a host and its microbiota and the adaptability of the microflora to local or regional food, we should start thinking about the sustainability of intestinal microbiota in cohorts of people not living on a 'Westernized diet', and attempts should be made to investigate or at least save feces from groups of people living on such food. As the first attempt, works should be started to collect and store feces from cohorts of people not living on a 'Westernized' diet. A proper place for storage could be the United Nation Global Seed Vault at Svalbard, Norway, or, if that proves to be difficult, a *novel, specially organized free International Cryobank of natural human Microbiocenoses* should be established. In the future, such samples may give us valuable guidelines if we want to go back to base-line again.

Dietary databases. Never before have that many people been on their move – from rural to urban areas – from country to country – and from one climate zone to another. As a consequence, never before have that many individuals changed dietary habits, never before has the need for more food been greater and never before have that large quantities of food been moved all around the world. Assumingly, these macro-scaled alterations create the main background for the observed increase in 'civilization diseases'. Obviously, there is a need for updated, reliable, and easily searchable information about food consumption in defined populations (84).

Environmental databases. All through life, man is virtually 'swimming' in an ocean of chemicals present in the biosphere. Recent reviews clearly underline that many groups of such environmental pollutants as phthalate esters (85), other endocrine disrupting chemicals, dioxins, hydrocarbons, and various groups of pesticides may influence upon epigenomic programing in many species, including *Homo sapiens* (85–89). A key problem is that reports often focus on genomic and/or epigenomic effects of one chemical or one class

of chemical whereas the human population, including pregnant women and infants, are exposed to a multiplicity of chemicals and additive effect(s) are far less investigated. Acetaminophen (paracetamol – the most commonly used 'pain-killer' in the industrial world), by acting on mitochondrial DNA may influence the development of some civilization diseases (81). Fortunately, epidemiological tools for evaluating probable health effects of exposure to multiple environmental factor problems are now under establishment (90).

More information in these four areas listed above will allow us to investigate epigenomic programing – and hopefully also epigenomic reprograming – on an individual base far more precisely than at present (49). Out of many future tasks, initial focus could be on:

1) Identifying epigenetically 'sensitive' region in the human genome.
2) Identifying more microbial, dietary, and environmental factors of importance and how they may interact on an individual as well as on a cohort level.
3) Identifying critical age-related 'windows' in which compound-related epigenetic programing may take place.

Future goals and problems

At present, health for all throughout life is nothing but a dream. However, accepting the fluid genome axiom and the postulate that many civilization disasters and diseases are 'man-influenced', we have been given the opportunity to interact. Working in parallel on the tasks outlined above, development of function foods represents reachable goals. Surely, 'no food fits all'. Therefore, specialized nutria-epigenetic and microbiota-epigenetic-based functional foods have to be developed (18, 63, 78, 79, 91). The intention is to have age- and cohort-related specialized functional foods that positively affect specific groups of hosts resulting in a decrease or elimination of negative consequences caused by the factors described above. Focus should be on foods to pregnant women and infants, and in these fields, much attention have been paid to the probiotic concept. In laboratory animals, it is well established that probiotics can perform epigenomic programing and some results indicate that this is the case also in humans (92). However, rules for such studies are not described in recent guidelines (93). The mere fact that most civilization disasters and diseases increase in incidence underline the importance of coordinating our effects in establishing an international platform 'Human Gut Microbiota and Epigenomics' that facilitates interdisciplinary collaborations among scientists and clinicians engaged in host microbial ecology, nutrition, metagenomics, epigenomics, and metabolomic investigations, as well as in disease epidemiology, prevention and treatment. It is not reasonable to think that our descendants will be impressed by our relatively little interest in this important field. If we are not increasing our efforts, we will be looked upon as if we are following an approach from pre-revolutionary France:

Apres nous, le deluge!

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