UDC 575.16:57.02

A. L. WANI[1] and A. ARA[1]

GENE-ENVIRONMENT MESHING: A PRIMORDIAL STEPPING TOWARD BEHAVIORAL MODULATION

Received Jun 20, 2014

Recent researches provide evidence that the early-life experience plays a significant role in human development, and this has also a role in the susceptibility to disease in later life. The mechanisms of how this works remain, however, largely in question. There is complex interaction between genes and environment, which is a critical feature of development and determines individual differences in future behavior. Studies on the genome-environment interplay gives rise to the new field of research called epigenetics. Epigenetic changes regulate gene expression without incurring any change in the underlying DNA sequence, relying instead on the chemical modification of DNA nucleotides and nuclear histone proteins. Epigenetics findings from human and animal studies suggest that the respective changes, in particular DNA methylation, are involved not only in cellular differentiation, but also in modulation of the genome function in response to early life experience affecting the gene function and the phenotype. Recent studies have demonstrated that heritable environmentally induced epigenetic modifications underlie reversible transgenerational alterations in the phenotype. In this paper, we review some recent studies regarding the gene-environment interplay. These studies provide new ways of thinking about the transmission of traits across generations and provide implications for our understanding of the origins of individual differences in behavior. Understanding of how the environment impacts the genome functions would have massive implications on how we approach solving current diseases and think about inheritance.

Keywords: genes, genome-environment interaction, epigenetics, behavior, DNA methylation, chromatin modifications.

Historically, there were always questions in the science, which initiate the debates on nature and nurture or genes and environment. Whenever, questions arise about the origins of individual differences in behavior, propensity, and the onset of diseases and disorders. The answer mainly came in the form that genes are exclusively responsible for all such outcomes. However, the outcome of different environmental interactions has led to more serious debates on such issues. Researchers in the recent few decades have made it more clear through critical analysis that studying the genes (genome) and environment individually limits our understanding of complex biological processes. The research works of the past decade made it clear that interaction between genes and environment is a critical feature of overall development, and more efforts are put on to research in order to understand the complexity of the interaction between genes and environment. The new understanding of gene and environment interaction gives rise to certain questions whose answers we need to understood in real means that what is the nature of genes, which allows them change? What sort of interaction is there between genes and environment, which brings in all the differences between the individuals? We can't simply underestimate the complex interaction between genes and environment. Scientists acknowledge the genome- and environment-related effects individually. We now need to realize and measure the potential interaction between them and the power of the outcome. Using of advanced tools and techniques to study G-E provides some insight into these issues. Perhaps, in future we shall get closertj this and may increase our understanding and answering the questions about the complex mechanisms of human behavior and transmission of the specificities of the latter from generation to generation. It can also help us understand the mechanism of heterogeneity or bias in the G-E

[1] Section of Genetics, Department of Zoology, Faculty of Life Science, Aligarh Muslim University, Aligarh, India.
Correspondence should be addressed to A. L. Wani or A. Ara (e-mail: anjumara.amu86@gmail.com).

interaction. The bias, which leads to variable outcomes, based on these interactions among the individuals. In this article, we discuss some breakthrough findings, which brought a major paradigm shift, and discuss the importance of actual understanding of the G-E interaction.

APPROACHES TO THE GENE–ENVIRONMENT INTERACTIONS

There was an old concept that both genome and environment considerably influence our behavior. Due to certain unavailability of modern sophisticated tools toward this aspect, it, however, remains almost unexplored. Due to recent advances, it became at present possible to detect genetic variations up to some extent. The variations leading to differences in the development among individuals are just begun to be understood.

Behavioral genetic studies were carried out for years using twin or adoptive samples and have been considered the standard for assessing the combined effects of nature and nurture in order to understand individual differences in human behaviors and traits. Behavioral genetic studies have revealed that, in general, more than half of the variations in individual behavior and traits are due to the environmental factors. These factors, which are typically unique across people in the same family (i.e., non-shared environmental influences), also make wide differences. There was a great number of adoption studies during the period of 1980s and 1990s. These studies have shown that genetic liability to antisocial behavior, as indicated through biological parent psychopathology and substance abuse, is only associated with the development of adult criminality and aggression under adverse adoptive environmental conditions. This indicates that neither nature nor nurture was solely sufficient and able, *per se*, to cause a pathology individually [1]. This whole scenario of findings led to the notion that environmental influences and experiences can exert profound effects on behavior. The underlying DNA structure and sequence, with which individuals have been born, do not change over time. However, there are variations in gene expressions in relation with certain environmental experiences. This leads to the development of a novel area of research called epigenetics, which aims to identify the factors that may alter gene expression and function across the lifespan.

This was the idea of Waddington in 1939, who suggested that diverse phenotypic outcomes may arise from the same genetic materials in different environments. In order to explain the origin of cellular differentiation and the establishment of structural and functional characters of different cells in every organism, he proposed the theory of epigenetics [2]. However, this theory was largely sidelined and did not attract much attention until recently.

The first report that showed convincingly that the environment has a direct influence on behavior of organisms, was published in 1958 by Cooper and Zubek [3]. They showed that rats selectively bred to be either “maze-dull” or “maze-bright” were reared after weaning in the environments “enriched” with increased sensory stimuli or environments containing “impoverished,” i.e., limited, sensory stimuli. These results demonstrated that the “early” environment presented to the newborn, which is the period of critical development for the young one, provides an evident change in the overall performance, like cognitive skills or skills for combating stress in their life. This study gave rise to new understanding, and a new field came into existence in order to study the genes and environment jointly and to measure the impact of different environmental factors on genes.

The relations between the serotonin levels and stressful life events were examined in a Dunedin’s longitudinal study [4]. This study analyzed how variation in a gene alters serotonin levels and exposure to stressful life events in determining risk of depression across a 20-year-long period. Alterations in the levels of serotonin within neuronal circuits may be related to the number and activity of serotonin receptors. The outcome of depression mainly appears first in the form of a mood change. These variations in mood have been associated with the state of the serotonin system, the system that is a target to most pharmacological interventions in the treatment of depression. No risk of depression as emergence of the genotype was observed when the stressful events were of a low intensity. However, when there was a high frequency of stressful life events in an individual’s life, individuals with a low level of the serotonin transporter gene variant are faced with a high risk of developing depression. Certain mechanisms lead to the development of resilience through gene/environment interaction, which can also lead to the variation in a risk or a resilience of neuropsychiatric disorders [5]. It is worth to note here that we must have to understand the interaction between the genes and environment

in its actual essence. As many environmental risk factors form only risks to particular people, many people surpass these so called risk factors very easily. For bringing this into research question, it is worth to understand what is that, which is variable? Gene, Environment, or the variable is overall interaction between the two?

EPIGENETIC PROGRAMMING: CONTROL ABOVE GENES

The studies mentioned above and various other empirical findings from G-E studies raise an important question: How the environment, which is outside, alters the effect of genes and leads to behavioral changes? How the environment alters elements of the brain and turns the latter disordered? How and why environments alter the impact of genes? To address these questions, we must first discourse the following question: What is the nature of genes, which allows them to change, and what is also the nature of that environment, which brings changes in genes? Since the discovery of the DNA functional structure, the biologists rely mostly exclusively on DNA in the genetic studies. In order to understand what is the role of DNA in individual's life and how it works, it may be very suitable to illustrate the example that genes can be likened to books, categorized, and arranged in such a way as in a library. Books and DNA both are "waiting to be read" [6]. If a book is difficult to reach or is hidden from view, it may *not* be read. Like an unread gene, an obstructed book is not altered or discarded. Both are still present, but if they are not accessible, neither the gene nor the book can be read. This may, however, take us to the notion that the genes may be present for all the information but, due to no access to the protein factors turning their information into a biological product, these genes remain in the so-called silent mode.

The process of recognizing the genes and their functions is going on. We expect that in future we shall understand much more about genes, and how there are variable genetic functions that lead to variable behavior. The gene that is not accessible to proteins, which read it, remains unexpressed. Epigenetically, many genes are covered by methyl tags that hide them from be accessed by proteins. In this manner, epigenetics can silence a gene [7]. DNA can become modified through the addition of a methyl chemical group to particular sites of nucleotides within the gene sequence. DNA methylation typically reduces the accessibility of DNA and can lead to «silencing» of the gene [8]. Advanced molecular techniques, such as examination of DNA methylation, modifications of histones, RNA editing, and RNA interference (e.g., micro RNA), have been developed and now allow researchers to explore the molecular mechanisms of epigenetic regulation [9-12].

EPIGENETIC MECHANISMS: DNA METHYLATION AND CHROMATIN MARKING

Epigenetic modifications are generally defined as changes in gene expression, which are caused by mechanisms other than changes in the underlying DNA sequence. In this case "epi-" means that these changes are realized above the DNA.

Great efforts have been put in studying the issues related to human psychiatric diseases; the results were, however, many time undefined. Epigenetics offers an exhilarating new frontier in the studies of human psychiatric and medical diseases, as well as psychological behaviors and traits.

Epigenetic phenomena are generally realized due to two mechanisms, DNA methylation and chromatin remodeling; the latter occurs via post-translational modifications (e.g., methylation, acetylation, phosphorylation, and ubiquitylation) of histone proteins. These proteins form a scaffold for the DNA helix.

Several epigenetic processes are essential to the overall development of organisms, like differentiation of the cells in a developing embryo during morphogenesis. However, certain epigenetic processes can have major adverse effects on health and behavioral outcomes. Some epigenetic changes remain restricted to one individual organism's lifetime. At the same time, there are studies on animal models, which suggest that other epigenetic changes can be inherited from one generation to the next [13, 14]. This way contributes, in part, to the heritability of behavioral traits and psychiatric diseases. A growing field of research suggests that environmental experiences, especially those related to stress, possess a significant capacity to alter biological and genetic mechanisms associated with an increased risk of behavioral problems. There are some important studies done recently and beginning to identify the precise mechanisms via which social environmental factors

can alter epigenetic programming. A study using animal models offers an exquisite description of how early environmental stressors can alter neurobiological responsivity to future stressful conditioning [15]. There are studies showing that the levels of DNA methylation change according to the age [16-18]. Other remarkable studies demonstrated that contextual fear conditioning also induces methylation changes in neural plasticity-related genes, in particular those of BDNF, reelin, PP1, and calcineurin [19-21].

Chromatin undoubtedly plays a major role in the storage and transmission of cellular information, but it seems a bit difficult to guess or analyze how it is evolved to become a system that responds to environmental and developmental cues and how it transmits information in response to daughter cells. We still know very little about how histones and other chromatin proteins interact with each other.

Chromatin marking, which has been the subject of a lot of evolutionary contemplation, is provided mostly due to methylation. It seems that this system was evolved primarily to defend cells against foreign and knave DNA sequences. Methylation of DNA, because of its working potential, seems to act as a part of the genomic immune system, in which cells detect foreign DNA sequences and render them harmless. This system is highly selective with respect to the G-E interaction, preferably when the environment is filled with vicious elements, like viruses or bacteria. When viruses invade a cell, they often hijack the host cells resources and multiply, and copies of viral-type DNA sometimes get integrated into the host's genome. If this happens or if the copies of the foreign DNA are present, the host cell is able to recognize them as foreign ones and to methylate them [22, 23]. The same treatment is given to knave certain DNA sequences, such as transposable elements multiplying and spreading within the genome rather like cancer cells within a body. They are also methylated and kept inactive. It is not known yet how the methylation machinery recognizes duplicated DNA sequences. These sequences, however, become easy targets for methylation because of the fact that such sequences can produce unusual paired conformations. Once methylated, the DNA attracts specific types of proteins, which bind to it and prevent its transcription. Obviously, keeping unwanted DNA sequences in check is essential if the cell lineages are to survive. Repeated sequences derived from foreign DNAs, which were situated in or around a gene whose product was not always required, can become signals for methylation and inactivation [18]. There is a problem with the general notion that the methylation system, being originated as a cellular defense mechanism, leaves, when examined, a lot of observations unexplained. It does not account for the observation that the methylation silencing machinery appears to come into play only when something else, such as chromatin remodeling through histone modification or the association of regulatory proteins, has already shut down gene activity. It seems that methylation silencing merely stabilizes and maintains an already established state, rather than being involved in initiating it. Another problem for the genome defense idea is that reduced levels of methylation in germ-line DNA were often found. The germ line is, however, a vulnerable place where defense is most needed, because the movement of transposable elements in germ-line cells could increase the burden of mutations in future generations [24].

Another recently discovered epigenetics mechanism mediated by micro RNAs is called RNA interference, which prevents unnecessary protein synthesis by binding to and degrading RNAs [25]. Epigenetic modifications directed by small RNAs have been shown to cause transcriptional repression in plants, fungi, and animals [26].

ENVIRONMENTAL INTERACTION AND ACTIVITY/ALTERATION OF THE GENE

Recent breakthrough in our understanding of the G-E reciprocity comes from studies analyzing epigenetic processes that are changing during the overall development with individuals experiences. The studies on rodents addressed important questions raised by the gene environment interaction: What is it that going inside the body from the environment and altering the impact of genes? In rodents, individual differences were found, which had been developed in them due to variations in maternal care they received during infancy. This variation in maternal care leads to variations in the expression of genes showing variable responses to the stress influences. The rodents that showed expression of low levels of glucocorticoid receptors in the hippocampus (i.e., in the brain region specifically related to learning and memory) demonstrated prolonged responses to stress. Analysis of DNA methylation within the regulatory region of the *GR* gene in individuals who got low levels of maternal care showed noticeably elevated levels of DNA methylation, and this circumstance

epigenetically silenced this gene [27]. The idea of designing epigenetic therapeutic drugs to target the epigenetic status is on rise nowadays. Besides this, the epigenetic effects are reversible, and their effects can be reversed by changing the environment [28]. There is also a possibility of removing the DNA methyl groups, which block the DNA from accessing by the proteins, by epigenetic drugs. The idea of creating epigenetic therapeutic drugs, which can demethylate the methylated genes, cannot be without risk; it should be taken into account that DNA methylation is a part of normal DNA replication in which certain genes in DNA are methylated. There are evidences of reversing the epigenetic status. Treatment with a drug that promotes increases in the DNA accessibility results in decreased *GR* methylation or/and in a dramatic shift in the phenotype of adult offspring who received low levels of maternal care [27]. When the drug increasing the level of methyl groups within the brain is used to the adult offsprings, those who had received sufficiently high levels of maternal care become indistinguishable from those who received low levels of such care [29]. This can be illustrated in other way; irrespective of age, individual experiences on changes in the environment affect the status of DNA methylation. DNA methylation is not always working to just add negative impact to our life; it works also in the other way. Many studies have shown that DNA methylation has a great importance [30]. The question now arises: Can we understand what proportion of DNA methylation is good, and what proportion is bad, and DNA methylation of which location in the organism is good, and which one is bad?

DNA methylation also helps in the formation of memory [30]. The learning experience is associated with rapid changes in methylation of the genes in the hippocampus, and if DNA methylation is inhibited, the individual will have a diminishing memory for the experience. It seems that DNA methylation serves as the reservoir of memory, which is formed through the experience in the course of life. It can be assumed that epigenetic mechanisms may help in shaping the genomic activity in response to the environment.

The quality of the environment can have significant effect on the overall development and the development of the brain. The prenatal period is characterized by rapid changes in the brain development. Within this period, the fetus is very sensitive because of being at a developmental stage. Any change in the environment can have a direct sustained effect on the functioning of the brain. It was shown that a regulatory region of the *GR* gene is associated with increased methylation in rodent fetuses having exposure of chronic stress during the first trimester of pregnancy [31].

When the mother is in stress, the hormones related to stress are transported from the mother into the fetus through the placenta, which can exert a direct influence on the fetal gene expression and overall development. The fetal overall behavior is determined by the mother's behavior. In simple words, if the mother is happy, the fetus may be happy, but if the mother is in stress, the fetus may be in stress. The diet of the mother has a major influence on the fetus, and variations in the mother's diet during pregnancy determine the overall major modifications of the fetal epigenome. A striking example of this phenomenon comes from the work in which a mutation of the *Agouti* gene in a mouse model leads to alterations in metabolism and the coat color. The level of DNA methylation of gene *Agouti* determines the severity of effects of this mutation. If the level of DNA methylation is high, it will epigenetically silence this gene and induce a «pseudoagouti» mouse phenotype that is comparable with that of a mutation-free mouse. It has, however, been found that the methylation status of this gene is altered when pregnant female mice with *Agouti* mutation fed on a diet rich in methyl groups. The offspring from such mice develop a pseudoagouti phenotype [32]. Thus, experiences leading to epigenetic factor-determined changes in the fetus are not limited to the postnatal period, but they start right from the womb of the mother. In other words, the mother during her pregnancy plays an important role in the epigenetic development of the foetus.

Chromatin modifications occurring at different times during the life of an organism have been associated with various short- or long-lasting regulatory events that affect the development and the functions of the brain and other tissues [33].

Sustained neuronal activity induces histone post-translational modifications in general and histone acetylation in particular, and these changes in nuclear proteins have been well documented. Procedures like electroconvulsive stimulation are one of the most effective treatments for major depression. Such procedures trigger histone modifications at promoters of the genes *CREB*, *BDNF*, and *c-Fos* (in particular, those show sustained changes in transcription), but not at promoters of other neuronal genes whose expression remains unchanged [34]. An increasingly large number of the experimental systems have documented alterations in histone post-translational modifications

in activity-dependent neuronal plasticity, addiction, and long-term memory formation [35-39].

The studies of genetically modified mouse strains, in which the function of specific histone-modifying enzymes has been altered in the brain, further revealed the fundamental contribution of chromatin remodelling to long-term neuronal plasticity and addiction [39, 40]. This class of changes in the brain leads, in general, to numerous changes in behavior.

GENE-ENVIRONMENT INTERPLAY AND ITS IMPLICATIONS FOR BRAIN BEHAVIOR-DETERMINING FUNCTIONING

In understanding the origins of individual differences in behavior among the individuals, we must need to understand the G-E interaction at deeper levels. A few crucial molecular processes related to this phenomenon have been described in laboratory studies. Increased DNA methylation levels in the promoter region of the *GR* gene were analyzed in cells extracted from the foetal cord blood. This increased DNA methylation suggests that the maternal depression and anxiety during the trimester may be the primary cause for the respective shifts in offspring, which leads to further consequences, like specific stress responses of three-year-old infants [41]. The brain is the principle organ showing increased levels of methylation due to the experiences in life. This increased DNA methylation leads to different outcomes, like serious mental illnesses. There are several studies, in which a variable DNA methylation in the brain tissue of suicide victims was found to be greater than that in the controls. High levels of methylation were detected in ribosomal RNA genes among suicide victims [42]. As the ribosomes provide synthesis of proteins, increased DNA methylation of ribosomal genes make them lower expressed, and this may lead to decreases in the levels of certain proteins. This may shape the problem more complicate, as if the proteins formed from such ribosomal genes are precisely those that read important genes. So, the epigenetic silencing of ribosomal genes can exert a silencing effect on multiple genes. Thus, studies about methylation of the ribosome genes can provide an insight about the later consequences. Studies of monozygotic (MZ) twins also provided important insights in understanding the epigenetic effects in humans. A 3-year-old and 50-year-old pairs of MZ twins were compared for gene expression. A higher level of discordance between the patterns of gene expression was found in older twins. This was associated with increasing differences in DNA methylation in older twins compared to those in younger ones [43]. This apparent discordance is most probably driven by specific environmental events. There are, however, twins also showing a great variation for the risk of a mental illness due to their variable epigenetic statuses determined by variable experiences obtained from the environment. A catechol-O-methyltransferase (*COMT*) gene analyzed for methylation patterns showed a varying degree of discordance in tissue samples from 5-year-old MZ twins; some MZ twin pairs demonstrated a high degree of discordance, while the epigenetic status in the others was very similar [44]. COMT is an enzyme involved in the inactivation of neurotransmitters (such as dopamine and norepinephrine), and disruptions in the respective neurotransmitter systems have been associated with many forms of psychopathology. In the twin pairs, a differential risk of neurodevelopmental disorder during later life can be predicted earlier by comparing and measuring the divergence of *COMT* gene methylation. What makes this interaction, and how the organisms (including human beings) interact with the environment? When developing in the same environment, how the twins show variations in the level of methylation and differential behavioral risk patterns? These are important questions to work for an answer. Assimilating epigenetic analysis in twin studies represents a novel approach to identification of the origins of individual differences.

TRANSGENERATIONAL EPIGENETICS

Transgenerational epigenetic inheritance is the idea that epigenetic marks (DNA methylation and histone modifications) can be acquired on the DNA of one generation and stably passed on through the gametes (sperm and eggs) to the next generation. In other words, experiences and environmental exposures can change the way the DNA works without changing the DNA itself, and this can be passed on to the offspring. An epigenetic alteration of the status of hypothalamic estrogen receptors in female offspring have been manifested due to variations in maternal care in rodents [45]. These receptors are critical in regulating maternal behavior and coordinate the sensitivity of females to hormonal cues. Increased estrogen receptor promoter methylation, decreased receptor expression, and succeeding decreases in the adult maternal

behavior of these offspring are all associated with the experience of the low level of maternal care in infancy. This is why individual behavioral differences in maternal care are transmitted across generations. The most interesting thing is that the females can alter this transgenerational inheritance by experiencing adequate-quality environmental conditions within later periods of development. Reductions in maternal care passed on to subsequent generations are the outcome of prolonged social isolation from peers and prenatal stress [45, 46]. Results of the above studies conducted on rodents demonstrated a limited genetic variability. Such studies suggest that not only genes inherited for having similarities in traits between parental and offspring generations, but something far more than genes is responsible for the described phenomena. Activated in response to environmental cues, epigenetic characteristics of DNA are dynamic, and these modifications are also stable and heritable. Thus, it is not only genetic, but both genetic and epigenetic factors, which are transmitted through cell lineages with consequences for the activity of genes within these lineages.

One of the most exciting areas of epigenetic research involves understanding of how environmental exposures to toxins (in a broad meaning) or chronic stress may cause epigenetic changes, and whether or not these changes can be transgenerationally inherited. Can stress in the mother or father impact the health of a child before they are even conceived? To get understanding of how the environment impacts on the genomic functions would have massive implications on how we approach counteracting current diseases and think about inheritance. In rodents, abnormal methylation patterns in sperm cells that are observed within several generations beyond the point of initial exposure are the outcome of a prenatal exposure to endocrine disruptors [47]. The environment also induces changes in the germ cells, and the latter can transfer them to the next generation through the mechanism of the germ-line epigenetic inheritance. The transmission of traits in such a mode is not inserted to DNA only, but also above DNA, which is epigenetic. Recent studies showed that certain psychiatric disorders, like phobic fear and other anxiety disorders, create memories in the brain of an individual. It was found that neurobehavioral disorders are memories in the brain attained by life experiences, and these disorders are transferred from generation to generation allowing the young generation to have the experiences of parents from their early age [48]. Such a phenomenon may contribute to the etiology and potential intergenerational transmission of a risk for neuropsychiatric disorders. The important question needing to be understood is the following: How information, which was in the brain, comes to be stored on DNA and, later on, to be transferred to the next generation? It is expected that the future research within this area will take us closer towards answering this question.

To bare out other epigenetic marks and modifiers, an extensive set of efforts is currently taking place, as epigenetic aberrations has been found to be as one of the major players in the pathogenesis of a number of diseases, like cancer, cardiovascular disorders, neuropsychiatric ones, and other complex diseases [49]. Almost all complex diseases are, however, multifactorial and/or polygenic in their nature, and most of the neurological and psychiatric disorders are considered to be complex. Despite huge progress in medical science within the last few decades, many neurological and psychiatric disorders remain mostly incurable. Pure genetic studies, even after using advanced high-throughput techniques (e.g., whole genome mutation analysis), failed to find the pathogeneses underlying of complex neuropsychiatric diseases [50]. Neurological and psychiatric diseases do not show a Mendelian pattern of heritability, and neuroscientists have been inspired to look for epigenetic aberrations. Furthermore, neurological and neuropsychiatric diseases (e.g., mood disorders and multiple sclerosis) usually demonstrate an episodic pattern and, often, complete recovery/remission for many years, which are not apprehended in genetic diseases. The organic bases of DNA (genetic codes) are fixed and stable, and, therefore, genetic diseases often have an early age of onset followed by chronic/progressive patterns. Epigenetic codes are flexible and dynamic; therefore, an episodic nature of illness presentation in the neuropsychiatric disease could be more compatible with an epigenetic dysregulation because of an intrinsic or extrinsic insult and/or action of environmental factors [12].

The research in epigenetics promises a great advantage for the future, particularly if we can understand the epigenetic basis of the inheritance of acquired characteristics. This might help us to develop a new therapeutic strategy for reversing the epigenetic effects. Also, there is a possibility of developing new methods of prevention for the following generations. The future research can direct us to the possibility of identifying the epigenetic biomarkers, which will

allow ones to detect early-stage diseases. Therefore, further understanding of interactions between the genes and environment with respect to epigenetics is important especially for the neurobehavioral and psychiatric diseases.

CONCLUSIONS

In this article, we have tried to highlight the evidence that there are vastly different environmental factors all able to alter gene expression during ontogenesis, to change the phenotype, and to modify the epigenome. Moreover, if the respective environmentally induced epigenetic adaptations occur at crucial stages of life, they can potentially change behavior of the individual, disease susceptibility, and survival. The failure of epigenetic gene regulation is known to often induce various rare congenital disorders. This is because the epigenetic tags cover the genes and prevent their expression, changing in such a way the normal epigenetic status due to the action of various environmental factors. This changed epigenetic status, however, is not restricted in the genome of a single individual but can be transmitted to the succeeding generations. This makes urgently necessary precise understanding of the interactions between genes and environment and, more specifically, of how they interact to bring changes, or of what are the conditions, which are prerequisites for a complex interaction between genes and environment possessing the potential to produce debilitating results. The mechanism seeming to be primarily responsible for such changes in the life of an individual is DNA methylation changes, which may drive human diseases and health problems. Nonetheless there may be a real possibility to reverse the aversive methylation modifications of DNA.

The challenge in the field of epigenetics is to determine the origins of heterogeneity between the individuals by exploring the relationship between genetic and epigenetic variations. There are other relevant questions, like how different individuals show variable epigenetic outcomes in the same environment. There are other basic questions to be addressed, like what are the pathways whereby specific experiences target and reach particular genes. This field of research certainly holds a promise in uncovering the nature of experience-dependent changes in the development both within and across generations. However, it can be hoped that the advancement of tools and techniques of research in the field of epigenetics can further help exploring the role of gene environment interplay within the broad field of neuroscience and other related fields.

This paper is a review of the published data, and confirmation of its correspondence to the ethical norms for experiments on animals and/or studies of humans is no necessary.

The authors, A. L. Wani and A. Ara, confirm that they have no conflict of interest with any organization or person that may be related to this study; there were also no conflict of interest in interrelations between the authors.

А. Л. Вані[1], *А. Ара*[1]

ВЗАЄМОВПЛИВИ ГЕНОМА ІЗ СЕРЕДОВИЩЕМ: ПОЧАТКОВІ КРОКИ ДО МОДУЛЯЦІЙ ПОВЕДІНКИ

[1] Мусульманський університет у м. Алігарх, Уттар Прадеш (Індія).

Р е з ю м е

У недавніх дослідженнях були отримані докази того, що досвід (комплекс впливів), отриманий протягом ранніх періодів життя, відіграє істотну роль у розвитку людини і що це також впливає на чутливість до захворювань у пізніші періоди. Механізми, які опосередковують такі впливи, залишалися значною мірою дискусійними. Існує складна взаємодія генома та оточуючого середовища, що є критичним фактором щодо розвитку та зумовлює індивідуальні відмінності поведінки. Дослідження взаємовпливів генома та середовища започаткували новий напрямок у відповідній області – епігенетиці. Епігенетичні зміни – це феномени, що регулюють експресію генів без будь-яких змін у послідовності ДНК та базуються на хімічних модифікаціях нуклеотидів ДНК та ядерних білків-гістонів. Досягнення епігенетики в дослідженнях людей та тварин дають підстави вважати, що епігенетичні зміни (такі, як метилювання ДНК) не тільки впливають на диференціацію клітин, але й модулюють функції генома у відповідь на впливи, отримані протягом раннього періоду життя, причому змін зазнають і функції генів, і фенотип. Результати недавніх досліджень показали, що індуковані середовищем епігенетичні модифікації успадковуються та є основою оборотних трансгенераційних змін фенотипу. Дана стаття являє собою огляд деяких нових робіт, присвячених взаємодії генома із середовищем. Відповідні досліди відкривають нові можливості для нашого розуміння причин індивідуальних відмінностей поведінки. Розуміння того, як середовище впливає на функції генома, знайде багато точок прикладання в підходах до лікування деяких хвороб та в ідеях механізмів успадкування.

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