We are not hostages of our genetics: epigenetics in the control of gene expression mechanisms involved with some diseases

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1 INTRODUCTION

Epigenetics is an emerging area of scientific research that shows how environmental influences induce genes, in a certain way, to express themselves according to the environmental context, which includes various factors, emotional experiences and lifestyle that actually affect the expression of genes.The most interesting part of epigenetics is perhaps its flexibility unlike mutations that can occur in DNA base pairs, epigenetic modifications occur all the time and are easily influenced by the environment in which the organism lives. Such factors range from complex and clearly harmful substances such as heavy metals, pesticides, radioactivity and cigarette smoke, to common substances present in our body such as hormones, bacteria and nutrients incorporated in the diet. Researchers have shown, in 2003, that according to the type of diet of the mother, the coloration and predisposition to obesity of mice can change. And that the mechanisms behind these changes are purely epigenetic, that is, all mice had exactly the same genes, the only difference was in the pattern of molecules associated with DNA.

Collaborators (2007), Felsenfeld and collaborators (2014), Haig (2011), Morange (2013), epigenetics in short, demonstrates that our genes do not exclusively define how we are, that is, in a broad sense is the tool of interaction between phenotype and genotype, and demonstrates that there are heritable changes in DNA that do not involve the change in genotype sequencing (GOLDBERG; ALLIS; BERNSTEIN, 2007). According to Bird and collaborators (2002), the gene expression of the phenotype also depends on the activation or deactivation of genes regulated by mechanisms such as DNA methylation and histone acetylation (NIGHTINGALE; O'NEILL; TURNER, 2006).According to Goldberg and collaborators (2007), part of the difficulty that epigenetics goes through is the lack of acceptance of definition as a specific research field, separate from genetics.Epigenetics, may come to explain how changes that make identical twins, who have the same DNA, may throughout life acquire different characteristics and express divergence on something that has strong genetic inheritance

(PETRONIS, 2006).The appearance of a cancer in only one of the identical twins, while the other takes a life without ever developing it, even with a greater predisposition from the genetic point of view (SBOC) is one of the topics to be explored.Epigenetics presents some answers that may explain these factors since we can define it as heritable changes in gene expression on the chromatin organization, which do not cause modifications in the sequence of DNA Bases.(GIBNEY; NOLAN, 2010).

1.1 THE ORIGINS OF GENETICS

The history of the first studies of the transmission of hereditary characteristics occurred prior to the discovery of the tools responsible for this, because Darwin when writing the origin of species, which has its first publication dated 1859, did not know the way in which the hereditary characteristics were passed down through generations.(EXLEY, 2009).Although we can mention that the main names had a very short interval between their theories (Darwin and Mendel), both never came to relate their work, but according to Galton (2009) records show that Mendel had access to the work of Darwin and when the presentation of his work was read in front of the society for the study of natural science of Brunn, in 1865.Darwin's book was already in its third edition, records point out that in 1863, Mendel had access to Darwin's publication in its second edition, and among the 40 prints he made of his article, which Mendel sent his work on experiments between plant hybridization to famous scientists of the time, some studies may have been addressed to Darwin, but ignored (GALTON, 2009).Charles Darwin through his theory of natural selection, made a quite correct prediction about the specialization and natural evolution of species (EXLEY, 2009).At the same time, in a monastery of the Augustinian order in the Czech Republic, Gregor Mendel was carrying out work on the crossing of plants, coming to define the laws that until today we are based about genetic crossing, known as Mendel's Laws (ILTIS, 2018). Despite his enormous contribution, his work was only recognized decades after his death, as it was ignored at the time of its publication.

1.2 THE DNA

Deoxyribonucleic acid is an organic compound whose molecules contain the genetic instructions that coordinate the development and functioning of all living things and some viruses, and that transmit the hereditary characteristics of every living being DNA, the material responsible for protein synthesis, is formed from molecules called nucleotides, consisting of a sugar-phosphate molecule and a nitrogen side chain, these nitrogenous bases are formed by four molecules (adenine, thymine, cytosine and guanine), which we can refer to as A,T,C,G.(COX, 2012).In all living organisms the rule is the same, with the exception of RNA molecules, which in place of thymine, has the uracil and also the main chain is formed by a sugar a little different, ribose, in place of deoxyribose.(ALBERTS et al., Also in the last century, according to the book DNA: The secret of life,

Watson and Crick (2005) there was a dispute to discover the structure of DNA, which was discovered by James Watson and Francis Crick as a double helix structure, with special contribution of Rosalind Franklin, who through its preliminary studies, defined what was being sought, unfortunately different from the other two names, she was not recognized in life for his work, being out of the Nobel Prize for the structural proposal of DNA.

1.3 POST-GENETICS

The discovery of the gene and the structure of DNA and its composition leveraged a new science, molecular biology, with the advent of new technologies, it became possible to study the interactions that occur between DNA, RNA, proteins and other organic compounds from the molecular point of view (BURLEY et al., 1999).With the study of DNA and the mechanisms of functionality, it was defined what is the genomic imprinting, which according to Reik and Walter (2001) is a specific expression of the allele depending on the parent of origin of the allele.

1.4 THE BACKGROUND BEHIND EPIGENETICS

Initially we must understand the context behind epigenetics, having been studied after an incident of great importance in the Netherlands, the so-called "Dutch Famine" which was a result of the Nazi occupation of the Netherlands at the end of World War II, where there were blockades that prevented the arrival of food to 4.5 million people, causing the death of 22 thousand people as a result. (FRANCIS, 2015).After this incident, several studies were initiated, which observed the inheritance resulting from this fact, but there were no changes in the DNA sequence itself, which raised doubts about how the inheritance was passed on to future generations, which led to the emergence of the term epigenetics, which basically means persistent changes that occur in DNA without leading to changes in genetic sequencing. Before the term epigenetics was coined, there was the term epigenesis, which was introduced by physicist and physiologist William Harvey, around the seventeenth century, which portrayed the ancient theory, in which the embryo already has since its "genesis" pre-formed parts of its limbs. (DEICHMANN, 2016).However, the term epigenetic was created to encompass its previous concept, giving more breadth to the subject, thus establishing a blend between its old meaning, and the new science of study on the development complex between the genotype and its phenotypic expression, the credit for coining and introducing this term, is given to Conrad Waddington, who in 1957 proposed the concept of an epigenetic landscape as the cellular decision-making process during its development (GOLDBERG; ALLIS; BERNSTEIN, 2007).Also according to Goldberg and collaborators (2007). Another concept of "epigenetics" was suggested by the microbiologist Nanney (1958). He divided himself between two concepts of cellular control system, one being the gene system

itself, and the other some mechanisms that help in what should or should not be expressed in the phenotype.

1.5 HOW EPIGENETIC CHANGES HAPPEN:

Before talking about the epigenetic alterations, we must mention that they occur in parallel to the gene expression, process in which occurs the transcription, where it is believed that most of the epigenetic processes occur, although they are also expressed during the splicing and translation (ROBERTSON, 2002).The epigenetic changes occur in chromatin, which is the complex formed by the double strand of DNA and histones performing its compaction and allowing the allocation of DNA within the nucleus of a cell, the epigenetic modes of gene regulation that allow modifying the chromatin, occur through two ways, DNA methylation, and modifications in histones.(DEICHMANN, 2016) Currently, research shows that methylation of chromatin occurs by interaction of a methyl-CPG binding protein. Which interacts with the repressor complex Sin3 / histone deacetylase(NG; ADRIAN, 1999).Didactically we can state, that the reconfiguration of chromatin during the process of DNA replication, is necessary for the activation or inactivation of gene expression, this replication process, is accompanied by the disruption of the genome, and reassembly of chromatin (GROTH et al., It is these mechanisms that converge to the current studies, besides the usual types of epigenetic changes most common in studies are methylation, acetylation, we can still mention phosphorylation, ubiquitilation and sumolization, which derive from more recent research, without a large scope of publications available, we can mention that all these processes are of natural origin and of great importance for organisms.(AHMAD; HENIKOFF, 2002).According to Reggie and collaborators(2012) In eukaryotes, DNA is packaged as chromatin in the nucleus and is subsequently organized into two different structural areas called silent heterochromatin and active euchromatin.

1.6 DNA METHYLATION

According to Leverson and collaborators (2005) DNA methylation is a covalent modification that activates hereditary gene silencing. We know that methylation is the most studied mechanism by which an epigenetic factor occurs, its distribution in the animal genome is very wide, and there is a great variety of patterns found in different animals, which creates the possibility that different distributions reflect different functions in the methylation system.

According to Nafee and collaborators (2008), approximately 3% of human DNA cytokines are methylated. Methylation occurs in mammals mainly in so-called CpG islands, which are regions in DNA where a cytosine nucleotide binds to a guanine nucleotide, and according to a computational analysis of the human genome, there are on average 29,000 CpG islands (Lander et al. 2001). Methylation patterns occur via DNA methyltransferases (DNMTs) which are a group of enzymes

responsible for establishing the methylation of dinucleotides, identified so far being four in mammals DNMT1, DNMT2, DNMT3a and DNMT3b.DMT1, for example, serves to maintain DNA methylation during replication by making a copy of the methylation pattern of the parental DNA strand (GIBNEY; NOLAN, 2010) however it may not fully explain the persistence of methylation patterns. DNA methylation can be observed in diseases such as cancer, mental retardation, psychiatric diseases, neonatal diseases, Alzheimer's disease, and others. The following is a summary of the molecular machinery associated with epigenomics, with a focus on cancer and oncology

1.7 HISTONE MODIFICATION

Another important tool by which epigenetic changes occur, is the post-translational covalent modification of proteins known as histones, which is a stable structure that limits the accessibility of DNA, and its binding partners (NG; ADRIAN, 1999), these modifications that occur, can and do directly influence the structure of chromatin, studies suggest that DNA methylation and histone acetylation are dynamically linked in epigenetic expression, and according Vaissière and colleagues (2012).Hypermethylation of CpG islands in gene promoters triggers deacetylation of local histones, thus there is an intimate communication between them(ROBERTSON, 2002).We can cite as an example of histone modification an enzyme found in a protozoan called Tetrahymena Thermophila, this enzyme acetylates histones, causing an increase in the growth of yeast, this protozoan has been the focus of intense studies in recent decades due to its potential in contributing to the genetics, usually this protozoan is found in freshwater lakes, ponds and streams.(PAN; LIN; ZHANG, 2021)

1.8 EPIGENETICS AND AGING

Before entering the world of diseases with epigenetic origins or relationships, we can talk about the biological process responsible for the progressive wearing out of all living organisms, known as aging.

Some current and still recent studies, the progressive changes caused with histone modifications and methylation in DNA, creates an altered accessibility in the genetic material, resulting in a defective gene expression, aiding the occurrence of problems resulting from aging, thus increasing for example, a greater susceptibility to diseases.According to Pal, Tyler and collaborators (2016), in studies with yeast, the conclusion was reached that the loss of heterochromatin, which was hitherto held as the most promising model on one of the causes of aging, was taken out of paradigm, heterochromatin was seen to be reorganized, having a loss of protein in histones, which in human primary fibroblasts, this reduced protein synthesis, was a direct consequence of the shortening of telomeres, the consequence of this is a genomic instability caused by more "relaxed" chromatin (PAL; TYLER, 2016).In addition to the changes caused in heterochromatin, the study also cites DNA

methylation changes during aging, a process of progressive decline in DNA methyltransferase DNMT 1 levels is known to occur, which needs further study to be understood, and its long-term effects, and it is hoped that new genome sequencing technologies can fill the gaps in this research.The epigenetic changes affect the telomeres, which according to Blasco, M. (2007) the shortening of the telomeres occurs concomitantly with aging, and according to Aubert and Peter (2008) is the central point of the occurrence of aging in the body, as a result of aging, a disease that has a predisposition to appear is cancer, which we will talk about later.

1.9 EPIGENETICS GENOMIC BASES IN PREGNANCY

The change in our genes throughout our lives are the basis of genetics; we know that the life we live and the food we eat can interfere with our genome and thus lead to diseases in the neonate, some factors involved: changes in hormone regulation pathways, epigenetic deregulation and intrauterine development.Iron or zinc deficiency can inhibit fetal growth by decreasing the activity of igf-1 and its receptors. During fetal age women are more vulnerable to develop deficiencies, therefore the encouragement to consume a varied diet and important supplementation.Zinc is present in over 300 enzymes and play a role in gene expression, studies have found that a decrease in zinc in pregnancy and during growth was associated with the development of diseases.

Epigenetic processes are considered important mechanisms by which the genome can respond to the environment. The plasticity of the epigenome during the early stages of embryogenesis/fetal development becomes susceptible to disturbances induced by factors such as malnutrition, hormones and others, which could alter gene expression and phenotype in the long term, thus epigenetics could explain how early life experiences can be retained throughout life.

While the fetus is still in formation, a certain increase in nutrients, especially vitamins and minerals, is required, which is also important during pregnancy. As well as vitamin B 6 (pyridoxine), vitamin B 9 (folic acid) and vitamin B 12 (cyanocobalamin), vitamin B 12 is involved in the development of the nervous system.

This complex system begins to develop in the womb and continues for years after the baby is born (Santos, 2022).

Folic acid, also known as vitamin B9, is one of the essential vitamins for babies in the first months of pregnancy. This is because the vitamin is responsible for the formation of the baby's neural tube, which produces the brain and spinal cord of the fetus during the first month of pregnancy, the most critical period for malformations due to insufficient intake of essential vitamins and minerals during pregnancy (SILVA et al. 2007).

The extensive study in genomics for a few decades now shows that the food consumed by the mother modulates which genes will be more or less active in the baby (epigenetics). With personalized

maternal nutrition, it is possible to make the baby's epigenetic metabolic programming so that he/she will have a lower risk of developing chronic non-communicable diseases, such as diabetes, hypertension, and even Alzheimer's in the future.

When the embryo is developing, there are two moments when "global deletions of the DNA methylation pattern" occur. At these times, the fetus is susceptible to variations in the supply of substances (from the methyl group) to restore the standard methylation process of its DNA, women use folic acid before conception and in the first three months of pregnancy. A daily intake of 400 micrograms of this vitamin can reduce the risk of neural tube defects in the fetus by up to 75 percent, which prevents cases of anencephaly, paralysis of the lower limbs, and urinary and bowel incontinence in the babies. This, in addition to different degrees of mental disability and school learning difficulties,maternal health during pregnancy plays an important role in defining the health and disease risks of the offspring. One hypothesis is that of maternal immune activation. This hypothesis argues that inflammatory disturbances in utero can affect fetal neurodevelopment. Several maternal inflammatory factors, including obesity, asthma, autoimmune disease, infection, and psychosocial stress, are associated with an increased risk of neurodevelopmental disorders. Nutrigenetic profiling is nothing more than the result of the analysis of a set of genes that give us information about certain characteristics of the patient.The genes analyzed influence how the body responds to certain nutrients and vitamins, and indicate predispositions to diseases, food intolerances and sensitivities.First, the analysis is done by nutrient genetic testing, with each type of test evaluating a specific set of genes.

1.10 EPIGENETICS AND CANCER

Current research has shown that epigenetic principle gene regulation, collaborates with gene changes developing cancer, according to Sharma et al. (2009) due to failures in maintaining hereditary marks of various signaling pathways, lead to diseases such as cancer, still according to his work, even though the genetic changes in the cancer process is widely accepted, may be epigenetic changes are the first factors associated with the onset of some cancers, recognize this and design therapies is the reason for further study on the subject. (LUND; LOHUIZEN, 2004b)

The pathway first explained, is the DNA methylation in cancer, while in normal cells, the cpg islands do not show methylation, when active as in tumor suppressor genes, accompany the marks of active histones. Causing that during oncogenesis, the promoters of tumor suppressor genes, become methylated (SHARMA; KELLY; JONES, 2010).

Aberrant reprogramming in the cancer epigenome is also another point highlighted by current studies, the cancer epigenome is known to be characterized by global changes in DNA methylation (SHARMA; KELLY; JONES, 2010),

According to Jones and Baylin, methylation is closely linked to cancer development; if on the one hand oncogenesis is promoted by hypermethylation of tumor suppressor genes, hypomethylation acts by affecting gene stability.

It is concluded that both papers report that there is a direct influence of epigenetic processes on the development of several types of cancers, thus the tumor microenvironment is seen as an epigenetic modifier; by focusing studies on its cause, it is easier to understand and design emerging cancer treatments based on inhibitors of epigenetic regulators; clinical agents that inhibit DNMTs or HDACs are undergoing clinical trials (Claus and Lubbert et al. 2003).

The clinical and theoretical tests, take as strategy the application of molecules directed to reverse the aberrations caused by tumor changes, do this by focusing on DNMTs and HDACs as targets at the epigenetic level, the so-called "epi drugs" (drugs of epigenetic activity), focus on sensitizing cancer cells, as in example, restoring the receptors of various proteins, such as the estrogen receptor, absent in cases of breast cancer. (KRISTENSEN; NIELSEN; HANSEN, 2009)

According to Mazzone and colleagues (2017) immune evasion acts being the main obstacle against the efficacy of immune therapies against cancer, as it makes long term tumor control inefficient, so in theory, epi drugs tend to act by causing immune recognition of tumors to be restored, preclinical studies being conducted, show that immunomodulatory effects can lead to selective immune regulation, thus a better understanding of molecular mechanisms by which the currently studied DNMTs and HDACs act is needed, with more emphasis on clinical trials being carried out by HDAC and ANTi (Histone deacetylases immunotherapeutic and DNA methyltransferase immunotherapeutic).

1.11 EPIGENETICS AND OBESITY

The field of epigenetics began with the study of predisposition to obesity transferred generations, so currently, the causal correlation between obesity and the epigenome is well understood and studied.Obesity is considered a public health problem worldwide, being related to the onset of various comorbidities, and also responsible for contemporary diseases, despite being a disease with its multifactorial etiology, if it is considered that epigenetic factors influence in parts, it is considered that the main cause is dynamic changes in DNA pattern due to restriction or supplementation with different nutrients, especially in the perinatal period (CAMPEÓN; MILAGRO; MARTÍNEZ, 2009) where there is a change in the methylation pattern of some genes, being increased due to caloric restriction, also according to the author, the continuous advances in the area causes a search for gene promoters susceptible to epigenetic regulation, the genes involved in this process were named as epi obesogenic, where they find a greater hypermethylation in promoter regions, causing metabolic diseases.According to Herrera and collaborators (2011) there is an emerging pattern of epigenetic effects acting through the CNS in response to obesogenic environment, being driven by specific neurobehaviors, studies have

been done identifying Locis (parts of genes responsible for some characteristic) related to obesity, but in the next topic, we will talk a little about the link between epigenetics and neuroscience Neurological degenerations with epigenetic principles

According to Tsankova and collaborators (2007), epigenetics is a crucial factor for the development of the nervous system. According to the author, the points that epigenetics is involved in are neurogenesis, neuronal plasticity, learning and memory, and other points not yet studied, The discovery is given by the common mechanisms associated with the epigenetic tool, changes that occur in histones and DNA methylation in the promoters of genes of these characteristics, as a result, these changes may be responsible for the development of disorders such as depression, addictions, schizophrenia, and cognitive dysfunctions.Fragile X syndrome is the most studied epigenetic alteration of neurological principle concerning epigenetic factors, it occurs mainly in males, by the presence of only one x-chromosome, its consequences are severe intellectual disabilities, such as behavior similar to the autistic spectrum and delay in verbal development. This alteration has been identified by the presence of several repeats of the trinucleotide CGG in the gene known as FMR1, associated with mental retardation, the presence of many CGGs causes methylation in the gene preventing the production of an essential protein called fragile X mental retardation protein, which then causes the neurological disorder.There are also studies currently trying to use epigenetic application tools and drugs for the treatment of Alzheimer's, depression and other neurological disorders (MENKE; KLENGEL; B. BINDER, 2012).

1.12 EPIGENETIC ADDICTIONS AND DEPRESSION

During this topic we will cover important studies on the ability of the brain chemical dopamine, as well as transmitting signals through synapses, to enter the nucleus of a cell and control specific genes. This completely changes the understanding of genetics and drug addiction. Intense cravings for addictive drugs like alcohol and cocaine may be caused by dopamine-controlling genes that alter the brain circuits underlying addiction. Interestingly, the results also suggest an answer to why drugs that treat depression must usually be taken for weeks before they are effective.

These important findings deconstruct some theories regarding genetics and bring a new view of epigenetic markers related to addictions and depression. Associating this with the Jean-Baptiste Lamarck theory that traits acquired through life experience can be passed on to the next generation We really can inherit traits that our parents acquired in life, without any changes in the DNA sequence of our genes. This is all thanks to a process called epigenetics - a form of gene expression that can be inherited, but is not actually part of the genetic code. This is where it turns out that brain chemicals like dopamine play a role.

All genetic information is encoded in the DNA sequence of our genes, and characteristics are passed on during the recombination of genetic material during meiosis-a process known as crossing over.Genetic information and instructions are encoded in a sequence of four different molecules (nucleotides abbreviated as A, T, G, and C) on the long double-helix strand of DNA. The linear code is quite long (about 2 meters long per human cell), so it is stored carefully wrapped up in histones

Inherited genes are turned on or off to build a unique individual from a fertilized egg, but cells also turn specific genes on and off constantly throughout life to produce the proteins the cells need to function. When a gene is activated, special proteins bind to the DNA, read the sequence of letters, and make a throwaway copy of that sequence in the form of messenger RNA. The messenger RNA then carries the genetic instructions to the ribosomes in the cell, which decipher the code and produce the protein specified by the gene.

But none of this works without access to the DNA. By analogy, if the DNA strand remains tightly coiled, you cannot read the information contained in the gene . Epigenetics works by unwinding the strand, or not, to control what genetic instructions are carried out. In epigenetic inheritance, the DNA code is not changed, but access to it is.

This is why the cells in our body can be so different, even though each cell has identical DNA. If the DNA is not unwound from its various protein spools called histones - the machinery of the cell cannot read the hidden code. So the genes that produce red blood cells, for example, are turned off in cells that become neurons.

The histone strand that the DNA of a specific gene coils is marked with a specific chemical tag, like a molecular post-it. This marker directs other proteins to "coil the tape" and unwind the relevant DNA from that histone (or not to coil it, depending on the label).

It is a fascinating process that we are still learning more about, but we never expected that a seemingly unrelated brain chemical could also play a role. Neurotransmitters are specialized molecules that transmit signals between neurons. This chemical signaling between neurons is what allows us to think, learn, experience different moods, and, when neurotransmitter signaling goes wrong, suffer cognitive and mental difficulties. Serotonin and dopamine are famous examples. Both are monoamines, a class of neurotransmitters involved in psychological illnesses such as depression, anxiety disorders, and addiction. Serotonin helps regulate mood, and drugs known as selective serotonin reuptake inhibitors are widely prescribed and effective in treating chronic depression. They are believed to work by increasing the level of serotonin in the brain, which increases communication between neurons in the neural circuits that control mood, motivation, anxiety, and reward. This makes sense, of course, but it is curious that it usually takes a month or more before the drug brings significant relief to depression.

Dopamine, on the other hand, is the neurotransmitter that acts in the reward circuits of the brain; it produces that "give me a high-five!" The burst of euphoria that erupts when we hit a bingo. Almost all addictive drugs, such as cocaine and alcohol, increase dopamine levels, and chemically induced dopamine reward leads to more drug cravings. A weakened reward circuit may be the cause of depression, which would help explain why people with depression may self-medicate by taking illicit drugs that increase dopamine.

Ian Maze, a neuroscientist at the Icahn School of Medicine at Mount Sinai, has shown in important research with his collaborators (Maze I. et. Al Nature. 2019)that serotonin has another function: it can act as one of those molecular post-its. Specifically, it can bind to a type of histone known as H3, which controls the genes responsible for transforming human stem cells (precursors to all cell types) into serotonin neurons. When serotonin binds to the histone, the DNA unwinds, turning on the genes that determine the development of a stem cell into a serotoninergic neuron, while turning off other genes, keeping its DNA tightly wound. (Thus, stem cells that have never seen serotonin turn into other types of cells, since the genetic program to turn them into neurons is not activated.)

This discovery inspired Maze's team to wonder if dopamine might act in a similar way, regulating the genes involved in drug addiction and withdrawal. In the April Science article they showed that the same enzyme that binds serotonin to H3 can also catalyze the binding of dopamine to H3 - a process called dopaminylation.

Together, these results represent a major shift in our understanding of these chemicals. By binding to histone H3, serotonin and dopamine can regulate the transcription of DNA into RNA and, consequently, the synthesis of specific proteins from it. This turns these well-known characters of neuroscience into double agents, acting obviously as neurotransmitters, but also as clandestine masters of epigenetics.

In another recent research ,(Maze, I. et. Al 2020). Maze's team naturally began to explore this new relationship. First, they examined the postmortem brain tissue of cocaine users. They found a decrease in the amount of H3 dopaminylation in the cluster of dopaminergic neurons in a region of the brain known to be important in addiction: the ventral tegmental area, or VTA.

This is just one intriguing correlation, so to find out if cocaine use really affects H3 dopaminylation in these neurons, the researchers studied rats before and after self-administering cocaine for 10 days. Just as in the brains of human cocaine users, H3 dopaminylation dropped in the VTA neurons of the rats. The researchers also found a rebound effect one month after taking the rats off cocaine, with much higher H3 dopaminylation found in these neurons than in control animals. This increase may be important in controlling which genes are turned on or off, rewiring the brain's reward circuits, and causing intense drug cravings during withdrawal.

Ultimately, it appears that dopaminylation - not just typical dopamine functioning in the brain - may control drug-seeking behavior. Prolonged cocaine use modifies neural circuits in the brain's reward pathway, making constant intake of the drug necessary for the circuits to function normally. This requires turning specific genes on and off to produce the proteins for these changes, and this is an epigenetic mechanism driven by dopamine acting on H3, not a change in DNA sequence.

To test this hypothesis, the researchers genetically modified histone H3 in mice, replacing the amino acid to which dopamine binds with a different one with which it does not react. This prevents dopaminylation from occurring. Cocaine withdrawal is associated with changes in the readout of hundreds of genes involved in rewiring neural circuits and altering synaptic connections, but in the mice whose dopaminylation was prevented, these changes were suppressed. In addition, neural impulse firing in VTA neurons was reduced and they released less dopamine, showing that these genetic changes were actually affecting the operation of the brain's reward circuitry. This may explain why people with substance use disorder crave drugs that increase dopamine levels in the brain during withdrawal. Finally, in subsequent tests,

It appears that dopaminylation ... can control drug-seeking behavior. To put it simply, the discovery that monoamine neurotransmitters control the epigenetic regulation of genes is transformative for basic science and medicine. These experiments show that H3-tagging by dopamine actually underlies drug-seeking behavior by regulating the neural circuits that operate in addiction.

And, equally exciting, the implications likely go far beyond addiction, given the crucial role of dopamine and serotonin signaling in other neurological and psychological disorders.

Looking ahead, it asks whether :

Whether these epigenetic changes can also occur in response to other addictive drugs, including heroin, alcohol, and nicotine. If so, drugs based on this newly discovered epigenetic process may eventually lead to better treatments for many types of addictions and mental illnesses and a possible Alzheimer's treatment.

Depression is an important public health issue due to its high prevalence worldwide. According to the World Health Organization (WHO), it is estimated that 121 million to 300 million people suffer from depression . There is a lot of evidence that shows chemical alterations in the brain of the depressed individual, mainly with respect to neurotransmitters (serotonin, noradrenalin, and, to a lesser extent, dopamine), substances that transmit nerve impulses between cells. Other processes that occur inside the nerve cells are also involved. It is worth pointing out that stress can precipitate depression in people with a predisposition, which is probably genetic; epigenetics provides information about how this predisposition occurs.

Depression does not have a specific cause , but can come from a combination of genetic , biological , environmental and psychological factors . One of the main risk factors for depression are

genetic factors , when you have a close relative with a mental disorder or a mood disorder can increase the risk .

This disease has been recognized as a hereditary disease. The estimated risk of the disease in first-degree relatives is 3 times higher than that of the general population (Mandelli and Serretti, 2013). Some studies report a 10-fold increased risk in siblings of affected individuals, other studies report a genetic influence ranging from 30 to 40% (Mandelli and Serretti, 2013).

Biological factors and genes have been studied and the data show that depression is a complex and highly heterogeneous disease, in which it involves the interaction of many genes, each contributing a small effect, and several environmental factors that can modulate and trigger the genetic predisposition (Mandelli and Serretti, 2013). Therefore, identifying these genetic variants can help minimize genetic susceptibility by monitoring and modulating these environmental factors that trigger depression.

The researchers, scientists at USP, used epigenetic modulators, drugs that are part of a complex system that controls the activation and shutdown of genes, in order to "erase" the consequences of stress and the epigenetic marks induced by it.

Exposure to stress is one of the factors that can trigger depressive processes. It alters certain epigenetic markers in the brain and causes changes in genes related to neuroplasticity, which is the ability of the brain to change itself in relation to experiences. This is because stress increases DNA methylation in these genes (addition of methyl radicals to the molecule). Methylation is a generally repressive mechanism: it causes the chromatin in the cell nucleus to become condensed, so it prevents the transcription factors from reading the information, and the gene is not transcribed. Most antidepressants on the market act by reducing this DNA methylation process.

One of the nervous system proteins studied by the researchers was BDNF (brain-derived neurotrophic factor), which is a neurotrophin with documented effect on regulating the plasticity of neurons, according to the research, stress can decrease BDNF expression, if signaling by BDNF is blocked, the effect of the antidepressant does not happen.

Therefore stress would increase the methylation of the BDNF gene, which would decrease its expression, and this reduction may be related to depressive behavior.

The group of researchers from Professor Sâmia Regiane Lourenço Joca's team, connected to the Department of Biomolecular Sciences of the Faculty of Pharmaceutical Sciences of Ribeirão Preto, observed that if they administered genetic modulators that inhibit DNA methylation, this process would not happen, therefore the levels of BDNF would be normal and there would be an antidepressant effect. If this antidepressant effect is related to the normalization of this methylation profile, conventional drugs take time to work because it takes time to eliminate the alterations caused by stress, so by doing a direct modulation of these epigenetic mechanisms, the effect would appear quickly. And

so, once again, the discoveries of how these epigenetic processes occur contribute to advances in better treatments.

1.13 EPIGENETICS OF EMOTIONS

Based on what epigenetics points out, we know that consequences of our own actions and experiences can affect the lives of our children - even before they could be conceived - can change how we choose to live.

The theory of epigenetic inheritance is controversial, scientifically, the only way to transmit biological information between generations is through DNA, but, according to this theory, the

and environmental influences - for example, smoking, stress, or diet - can cause genetic changes in our offspring and play an important role in their development. Genes are changed by the influence of the environment through a "chemical label" (the epigenome) that adheres to the DNA and works as a switch: it modifies the expression of genes, activating or silencing them. (VALENTE; BARBOSA; RODRIGUES;

VIEIRA; BARBOSA, 2014) Changing our conceptions, feelings are now part of our anatomy and many of them, like physical traits, are inherited. In 1992, Moshe Szyf (molecular biologist and geneticist) and Michael Meaney (neurobiologist), began discussing inherited traits. Meaney believed that some feelings could be passed from one generation to another by genes in the brain, according to him, when parents experience some life-changing situation they would develop some change in their brain that could lead to some epigenetic change.

According to current studies in epigenetics, changes in diet, exposure to certain elements of the environment, intensities of relationships, and the ways in which we live our lives can alter our DNA, and with this, Professor Meaney's hypotheses have created a new arm of the sciences: the study of epigenetic behavior. This means that when our previous generations experience traumatic moments, our behavior is altered according to the stimuli developed by this trauma, affecting our decisions, perspectives, emotions and feelings.

The environmental information recorded by an ancestral generation can be transmitted to offspring by two routes: social transmission and biological inheritance. Social transmission involves a direct interaction between ancestral and descendant generation or an indirect interaction through maternal rearing environments that influence descendant biology. A characteristic of social transfer of information is the reversibility of effects when (a) such interactions and rearing environments mentioned above are manipulated through cross-adoption studies, or (b) the effects are no longer observed across multiple descendant generations. In contrast, biological inheritance speaks to the idea that gametes (sperm and eggs) are marked by the salient environmental event and that these marks are then inherited by offspring.In vitro fertilization (IVF) is used to generate offspring generations, (b)

should not be reversible when the rearing environment is manipulated as is done in cross-adoption projects, (c) persists in multiple offspring generations that are far removed from the disruption of the ancestral environment.

Some studies have also sought to understand the relationship between various psychiatric conditions and epigenetic changes, such as that of Perroud et al. (2016), whose work investigated whether there is a relationship between the effect of maltreatment in childhood and attention deficit hyperactivity disorder. Based on the measurement of the state of DNA methylation in a particular gene (5-HT3AR) in individuals who were exposed to maltreatment in childhood, and who present, in adulthood, conditions such as borderline personality, bipolar disorder, and attention deficit hyperactivity disorder, these authors claim that the epigenetic alteration of the gene in question is involved in the mechanism that links maltreatment in childhood with the severity of psychiatric conditions in adulthood. Day and Sweatt (2011) discuss, from a literature review, the evidence of an "epigenetic code" that mediates synaptic plasticity, learning and memory in the central nervous system. There is also other research (Keverne & Curley, 2008) that discusses how epigenetic processes may have been crucial in shaping the evolution of the mammalian brain in the prenatal period, as well as the behavior of these organisms. According to these authors, the mother provides the most significant environmental influence for the developing fetus, shaping brain development by producing long-term epigenetic modifications in neural and behavioral phenotypes.

Advances in fields such as neuroscience (e.g., Costa, Baxter, & Byrne, 2020) and Epigenetics (e.g., Carrell, 2019; Gescher et al., 2018; Tiffon, 2018) suggest that the data they find have the potential to describe how an organism is modified by its interactions with the environment, thus providing a more complete picture of such interactions, as Skinner anticipated. Since at least the Canonical Papers (1988), behavior analysts have become aware of discussions of Epigenetics. The pertinent question about what, after all, is modified when we talk about a "modified organism" finds new elements for discussion, especially after the data from the last two decades of research in Epigenetics.

2 OBJECTIVE

The present work has the objective of succinctly demonstrating that the genetic inheritance of an individual should not be a limiting factor .

3 METHODOLOGY

This was an integrative literature review; this technique happens when published articles are analyzed and bring discussions about an investigated phenomenon. It is worth mentioning that this type of study is important in the communication process, because it offers knowledge to several areas of activity, quick access to relevant results, because one of the purposes

This research is together with the literature to understand and reinforce the importance of research to support decision making (MENDES; SILVEIRA; GALVÃO, 2008).

This method allows the exploration of a given subject, in order to recognize the current state of the studied theme and point out knowledge gaps. The guiding question that directed this research was: Epigenetics in the control of gene expression - mechanisms involved with some diseases.

To obtain the data, the collection took place in October 2022, by searching the database: Coordination for the Improvement of Higher Level Personnel (CAPES) - Google Scholar, Latin American and Caribbean Literature on Health Sciences (LILACS), Scientific Electronic Library Online (SciELO) and Online System for Medical Literature Analysis and Search (MEDLINE). The Portuguese descriptors Dna, Epigenetics, gene expression, and gene expression were used to identify and locate the publications.

The inclusion criteria for selection were: articles available in full text, articles in Portuguese language and that dealt with the theme addressed. Exclusion criteria were: articles published only in abstract, duplicate articles, letters or editorials, dissertations and thesis and that were not within the theme addressed.

Only articles that focused on the theme in question were selected for analysis; the survey of these articles occurred in October 2022. Initially, the search was performed with the descriptors in the CAPES Periodicals by Google Scholar, and 212 publications were found, and after performing the filters established by the inclusion criteria, 100 publications remained, after analysis of titles and abstracts, exclusion by escaping the theme and repetition were selected 52 for reading inclusion analysis, finally, these articles were selected through content analysis, 21 articles to be included in the review

Finalizing the methodological path, the selected articles were analyzed. Based on the exploratory reading of the articles, it was possible to identify information that is similar in the results and discussions of the texts, and to better understand the data, the analysis categories of the study were built, listing the themes that appeared most in the reviewed articles, themes of extreme importance that address the importance of epigenetics in controlling gene expression.

4 DEVELOPMENT

The present work has the objective of succinctly demonstrating that the genetic inheritance of an individual should not be a limiting factor.

No one inherits cancer, obesity, or other diseases. Genetic inheritance does not make anyone a hostage to their genes, but what we do inherit are susceptibilities that, in conjunction with the lifestyle we adopt, will cause these genes to be expressed or not.Thus, through our lifestyle habits we are able to modulate our genes.Epigenetics describes molecular events that occur in DNA, but do not affect the

DNA sequence itself.In fact, it is now known that genetic activity can be regulated like a light bulb switch: it can be turned off or on, at different levels.This regulation is accomplished from chemical changes in the DNA sequence of our genes, without changing the identity of the base pairs that make up the DNA, literally acting on the genes, hence the term 'epigenetics. Epigenetic changes impact the way the DNA molecule is formatted, and consequently regulates which genes will remain active, influencing the physiology and behavior of an organism.Involving the study of an immense diversity of biological phenomena, through a literature search, we present the main points of relationship with cancer, addiction, obesity, neurological disorders, aging, and other applications to epigenetics in the control of gene expression and its mechanisms involved with some diseases. Among DNA methylation, the main tool by which epigenetics acts, in the end we relate the future perspectives and applications of epigenetic therapies as a way to demonstrate that we are not hostages of our genetics! Our free will and our choices govern our lives.

5 FINAL CONSIDERATION

With the results posted above, there is evidence that epigenetic disorders relate to and give rise to several significant human diseases. We believe that the study of the epigenome warrants as much research as the study of the genome. We are convinced that the field of epigenetics has immense potential for new discoveries that will help us better understand human diseases and possibly provide new approaches to cure them. Several aspects of epigenetic marks are of particular interest to researchers: they are specific to particular genes, they are influenced by the environment, they are dynamic and reversible, but they can nevertheless remain stable over generations.Recent studies have focused on the development of functional therapies that can reverse or cause selective expression through DNA methylation, and epigenetics represents the future of treatments and disease prevention, with more studies and research needed in the future, with clinical trials and drug applications; hematological alteration drugs have already been approved for use by the FDA.Unfortunately, early development is vulnerable to unwanted changes, making clinical trials in humans more complicated to carry out, and usually animal testing is chosen, but animal testing is not always effective due to some genetic differences, and the use of animals for experiments has become increasingly abhorred, due to the cruelty of some tests to which they are subjected.It is evident that there is a lot of room for learning about these factors, and the help that this area will have for the therapeutic future is very promising; the contributions to the treatment of human diseases and their mechanisms tend to be the future of medical science. Hopefully, continued research will enable major breakthroughs in the next decade. Revealing how epigenetic marks work and what they do will certainly open important new chapters in genetics and human health

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