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Applications and Perspectives of Epigenetics in Applied Biology and Biotechnology: A Review

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ABSTRACT: Every cell in the human body or other eukaryotes contains precisely the same DNA as the original fertilized zygote. Different cells transcribe and translate different parts of the genome and differentiate stem cells into different types of specialized mature cells. So, here the role of the various phenomena that take part in the body is named epigenetics- "Epi" means upon or in addition with genetic function. In our body, all differentiation processes are driven and maintained/sustained by epigenetic mechanisms, excluding the B and T cells of the immune system. Eukaryotic genetic control via epigenome comprises DNA methylation, RNA mediated silencing and histone modifications. Cell differentiation is a complex process related to both intracellular and extracellular signals, so epigenetics has a crucial role during the differentiation process. Precedently, researchers have struggled to understand the complex molecular mechanism to regulating the different chronic diseases. With the advancement and evidences available indicates that epigenetics studies are significantly increasing our knowledge about different diseases and its application in diverse biological fields. Thus, this review primarily focuses on the genetic and epigenetic markers relation and their malfunctions relating to chronic diseases and epigenetic medicine to cure some epigenetic errors. Additionally, it also discusses about the role of epigenetic modifications in improving biofuelproduction.

Keywords: Bioethanol,Cancer, Epigenetics, Genetics, Methylation.

INTRODUCTION

The human genome has been sequenced thousands of times; however, identifying genomic variations across different types of cells that contribute to health and ailments remains a significant challenge (Lander *et al*., 2001; McPherson *et al*., 2001). According to the central dogma of molecular biology, genetic information typically flows (1) from DNA to DNA by a semi-conservative replication and (2) from DNA to protein during its phenotypic expression in an organism (Snustad and Simmons, 2011) (Fig. 1). There are two steps in the transfer of genetic information from DNA to the formation of protein:(1) transcription, that is, conveying genetic information from DNA to RNA (which acts as a messenger), and (2) translation, involving the transfer of data from RNA to protein (Snustad and Simmons, 2011). Transcription is when one strand of DNA of a gene is used as a template to synthesize a complementary antiparallel strand of RNA known as the primary transcript. After that translation occurs, the sequence of nucleotides in the messenger RNA is converted into the sequence of amino acids in the polypeptide gene product (Snustad and Simmons, 2011).

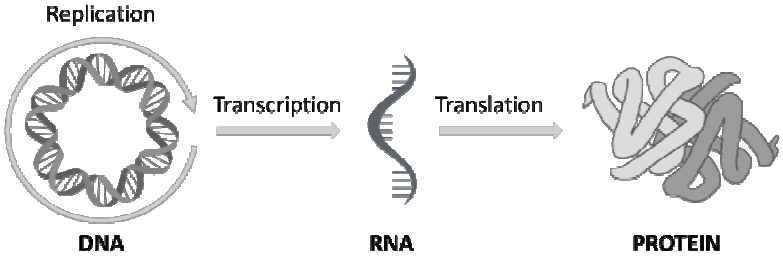

Fig. 1. The Processes of Central Dogma of Life.

Although all cells in an organism have the same genome, their functions differ due to quantitative and qualitative variations in gene expression. Therefore, controlling gene expression is fundamental for the development and differentiation of cells (Gibney and Nolan, 2010). Since every cell of eukaryotes has the same genome, different cells produce only the RNAs and proteins to carry out their needed specialized functions. There must be some new phenomenon occurring in eukaryotes responsible for this characteristic's different labour of the cells. Epigenetics is the study of cells regulating gene activity without altering the DNA sequence (Medline Plus Genetics, 2021). The mechanism of embryonic development was the initial definition of epigenetics (or, rather, "epigenesis"). A Greek philosopher, Aristotle (384-322 BC), postulated that the formation of an embryo is from the miniature version of itself in which epigenesis has the role in the gradual formation of an embryo from an amorphous starting point as an alternative to preformation (Ennis and Pugh, 2017). In a paper published in 1942, Conrad Waddington merged the older term "epigenesis" with "genetics" to form the new word "epigenetics". He defined it as the causal associations formed between genes and their products that go for the phenotypic expression.

Waddington recognized that different cells always contain additional epigenetic features, which he named "landscapes", and that cell differentiation always involves the change in this said landscape (Waddington, 1942). Every mature cell type has a unique pattern of gene locations within the nucleus that reflects its specific epigenetic landscape and gene activation pattern. According to more conservative modern definitions, "epigenetics" should refer only to mitotically heritable factors that interact with the genes (Ennis and Pugh, 2017). For several years, epigenetic information had been assumed to be limited to cellular divisions. But now, it is evident that epigenetic processes in organisms are inheritable and, therefore, can be passed down to another generation (Chong and Whitelaw, 2004; Liu *et al*., 2008).

Epigenetic mechanisms viz regulation of any gene expression circles around the DNA bases/histone protein chemical modifications. DNA is negatively charged and is wrapped around histone protein which is positively charged. Histone protein contains two copies of each of the histone proteins H2A, H2B, H3, and H4, making an octameric structure (Quina *et al*., 2006). These proteins have a globular domain and flexible (relatively unstructured) "histone tails", which protrude from the surface of the nucleosome (Allis *et al*., 2007). The nucleosome is a nucleoprotein complex that packs the DNA and is the basic repeating unit of chromatin. The DNA in between the repeating nucleosomes is the linker DNA stabilized by the histone protein H1. Chromatin is further condensed via the non-histone proteins, leading to chromosome formation during the mitotic phase of cell division. The chromatin part, which is loose and transcriptionally active, is called euchromatin, while the dense and transcriptionally inactive part is called heterochromatin (Li *et al*., 2007). The three principal epigenetics methods are DNA methylation, histone modifications (acetylation, phosphorylation, methylation, etc.), and non-coding RNA-based mechanisms. These three mechanisms are distinct but are interrelated and control gene expression (Ennis and Pugh, 2017).

DNA Methylation. The methyl group is a minor epigenetic modification known. A DNA methyltransferases (DNMTs) enzyme catalyzes the covalent bonding of this molecule, which has three hydrogen atoms attached to one carbon atom, to some of the DNA's Cytosine bases (C) onto the C5 position (Ennis and Pugh, 2017). The DNMT family have DNMT3A, DNMT3B, DNMT1, and DNMT3L,in which DNMT3L lack any inherent enzymatic activity, whereas the other three are active on DNA (Kareta *et al*., 2006). DNMT1 encodes the methyltransferase for maintenance, while DNMT3A/DNMT3B encodes the de novo methyltransferases needed to maintain and establish genomic methylation. The mitotically heritable methylation process of DNMT1 is critical for maintaining the epigenetic landscapes of mature cells and preventing cell differentiation reversal (Okano *et al*., 1998; Okano *et al*., 1999; Ennis and Pugh, 2017). DNA methylation is more like a censor's, which is telling the cell "Nothing to see here" means causes gene silencing (Ennis and Pugh, 2017) (Fig. 2).

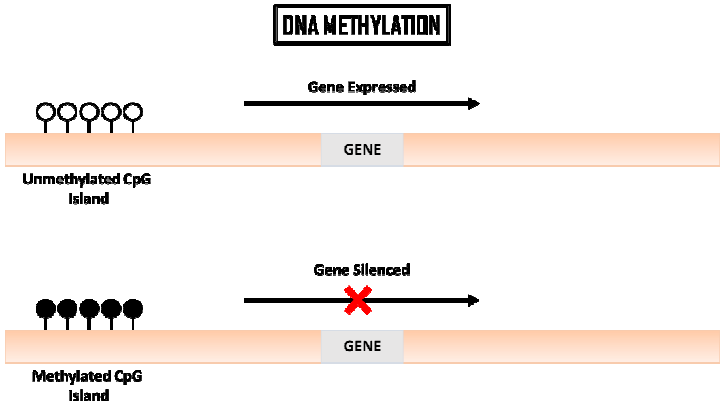

Fig. 2. Role of DNA Methylation.

DNMTs are involved in the stabilization of the genome, particularly repetitive sequences, i.e., problematic because they can move to new locations and can make the transcription and DNA replication machinery slip and stumble, causing mutations that lead to cancer and other diseases (Ennis and Pugh, 2017; Okano *et al*., 1999). DNMTs are needed for the transcriptional silencing of several sequence classes, including genes on the inactive × chromosome, transposable elements, and imprinted genes. Their silencing is necessary for the integrity of the chromosome (Robertson, 2005). Methylation of DNA does not happen at random but instead follows a set of rules and patterns. Most methylated Cs are adjacent to G bases. Many active genes have a cluster of these around their transcription start sites; in other words, observable data says around 70% of genes promoter regions had high CpG concentrations. The cluster features called CpG islands are mostly unmethylated, but, CpGs between genes or in repetitive DNA sequences are usually methylated (Saxonov, 2006; Ennis and Pugh, 2017). There is a six-membered family of methyl-CpG-binding proteins named MBD1 (methyl-binding domain 1), MBD3, MBD4, MBD2a, MBD2b, and methyl-CpG binding protein 2 (MeCP2) in the cell nucleus recognize and bind specifically to methylated C bases (mC). These proteins inhibit transcription from methylation of DNA-containing genes, preventing the generation of the relevant RNAs and proteins (Fan and Hutnick, 2005; Klose and Bird, 2006). When both strands of the DNA double helix are methylated at the same CpG site, transcription silencing occurs (Ennis and Pugh, 2017). Recent discoveries reveal that undifferentiated stem cells (embryonic stem cells), despite CpG cytosine methylation, had non-CpG cytosine methylation which is pivotal for gene regulation (Lister *et al*., 2009). However, DNA methylation does not work alone; other forms of epigenetic modification also aid in gene activation/silencing.

Histone Modifications. Post-translational modification to histone proteins is the second epigenetic mechanism. Most modifications are added to histone tails, and histone modification patterns change more frequently and quickly than DNA methylation patterns. They are linked to short-term fluctuations in gene activation patterns rather than the longer-term changes mediated by DNA methylation. These modifications include enzyme-catalyzed methylation,acetylation, ubiquitylation, ADP ribosylation, phosphorylation, deimination, proline isomerization, and sumoylation (SUMO) methylation and acetylation have been most studied. Higher-order chromatin structure is defined by acetylation and methylation modifications, which result in gene repression or expression (Jenuwein and Allis, 2001; Ennis and Pugh, 2017; Alhamwe *et al*., 2018). Histone phosphorylation is a well-understood modification linked to DNA repair and transcriptional activation. Histone ADP-ribosylation appears to work similarly to acetylation in that it physically disrupts the nucleosome structure, making it easier to transcribe the DNA. Depending on the attachment site, SUMO and ubiquitin proteins appear to be linked with both silencing and activation of a gene. Identifying and then comprehending additional histone modifications is a very active and ongoing area of research (Mellert and McMahon, 2009; Ennis and Pugh, 2017). Meanwhile, the 'Histone Code Hypothesis' proposed that a combination of different modifications of histones define individual epigenetic markers that could collectively generate plasticity in the expression of the gene among organisms (Strahl and Allis, 2000; Jenuwein and Allis, 2001).

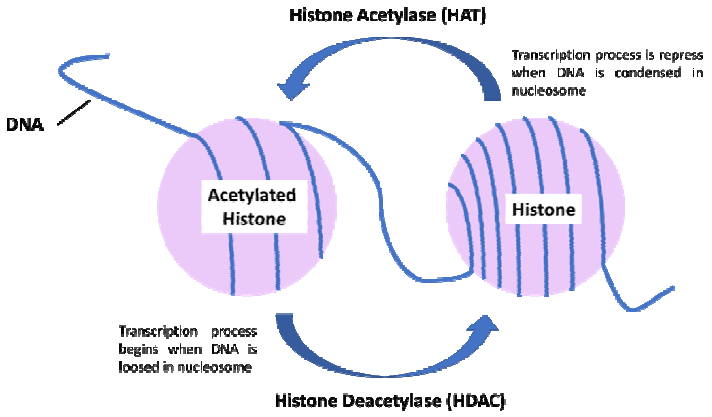

Fig. 3. Histone Modification: Acetylation.

The acetylation of lysine residues is a thoroughly well-studied histone modification. It is a reversible process that is catalyzed by two enzymes that are histone deacetylase (HDAC) and histone acetylase (HAT). In the presence of an acetyl group, the interaction between the positively charged histone tail and negatively charged DNA reduces, resulting in a less condensed nucleosome, allowing transcription factor complexes easier access (Feng and Fan, 2009). Likewise, HDAC removing the acetyl group leads to gene transcription repression (Fig. 3). The number of methyl groups (mono, di, or tri) added to the lysine residue determines the effect of histone methylation; for example, H3K4 (histone3, lysine4) tri-methylation is linked to the activation of the transcription process, while the trimethylation on H3K9 or H3K27 is associated to

transcriptional repression (Kouzarides, 2007; Mau and Yung, 2014). Histone demethylation is a process that can reverse histone methylation (Shi *et al*., 2004; Klose *et al*., 2006).

Non-coding RNA. Not all RNA strands copied from the DNA template during transcription are translated into proteins; some have unique functions, such as epigenetic regulation of post-transcriptional gene expression. The non-coding RNA (ncRNA) molecules consist of less than 30 nucleotides length microRNAs (miRNA) and short interfering RNAs (siRNA) as well as ≥ 200 nucleotides length long non-coding RNAs (lncRNA) (Wei *et al*., 2017; Ennis and Pugh, 2017). The majority of regulatory RNAs are only produced in specific cells, at particular stages of development, or in response to changes in the cell's environment, such as bacterial infection. Each cell's unique combination of regulatory RNAs helps to determine which genes are transcribed and which proteins are produced (Ennis and Pugh, 2017). Some miRNAs have a role in RNA interference (RNAi) machinery by binding to its target mRNA, resulting in decreased translation level (by directing it to suppression or degradation) and thus reducing the stability of those transcripts. An individual miRNA can target many different mRNAs, and many other miRNAs can inhibit the translation of a single mRNA. RNA polymerase II (pol II) transcribes miRNA genes into primary miRNA transcripts, which must be processed further before being exported from the nucleus (Lee *et al*., 2004; Ennis and Pugh, 2017). Histone modification, DNA methylation, and ncRNA are epigenetic regulation processes regulating gene transcription and allowing active or silent chromatin states to spread from their initial location to adjacent genes and beyond (Ennis and Pugh, 2017) (Fig. 4).

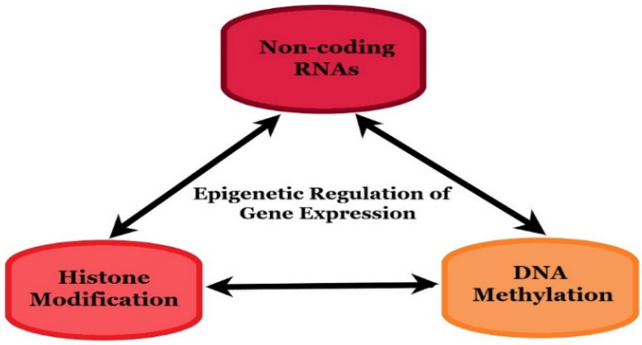

Fig. 4. Epigenetic regulation of gene expression.

Many species, including mammals, have transcriptional gene silencing and DNA methylation activity from the action of siRNA on it (Morris, 2009). lncRNAs play a crucial role in imprinting and X-chromosome inactivation to direct each type of epigenetic modification related to the chromatin (Rinn *et al*., 2007). Both lncRNAs and siRNAs have been shown to regulate gene expression through heterochromatin formation (Chisholm *et al*., 2012; Frías-Lasserre and Villagra, 2017). Hence, altered gene activity caused by genetic and epigenetic errors is the common cause of genetic disorders and chronic metabolic and degenerative disorders.

CHRONIC DISEASES LINKED TO GENETICS AND EPIGENETICS

Genetic and epigenetic marker role in obesity. Obesity and overweight, according to the World Health Organization (WHO), are defined as abnormal or excessive fat accumulation that poses a severe health risk. The body mass index (BMI) is a simple demographic measure of obesity, which is calculated by dividing a person's weight (in kilograms) by the square of their height (in metres) (World Health Organization [WHO], 2020). The body mass index (BMI) is a metric used by doctors to measure if a person's weight is average for their age, gender, and height. Overweight is a BMI of 25 to 29.9, while obesity is defined as a BMI of 30 or higher (WHO, 2020). The waist-to-height ratio (WtHR), waist-to-hip ratio (WHR), and the amount and distribution of fat on the body are all elements that determine a person's weight and body shape. Obesity and excess weight can put a person at risk for various health issues, including metabolic syndrome, which includes type 2 diabetes, certain types of cancer, hypertension, and many cardiovascular diseases (*Figure. 5*). Some main reasons for obesity in the human population are consuming too many calories, leading a sedentary lifestyle, not sleeping enough, some medications, self-perpetuating nature, obesity genes, and aging (Srikanth *et al*., 2019).

In case the genetic reasons there are recent technical advancements, as well as substantial increases in the scope and statistical precision of genome-wide association (GWA) studies, have facilitated the identificationof similar genetic variants related to obesity, adult BMI risk that has been routinely replicated in various populations (Elks *et al*., 2010). Frayling *et al*. (2007) identified the first such common genetic variation related to adult BMI in the FTO (fat mass and obesity-associated) gene region, which has neuronal function linked with control of appetite in 2007, and it has been associated with causing type 2 diabetes (Zeggini *et al*., 2007). This was closely followed by variation downstream of MC4R (melanocortin 4 receptor gene) in 2008 (Loos *et al*., 2008). Meanwhile, MC4R is linked with waist circumference (WC) in individuals of Indian Asian or

European ancestry (Chambers *et al*., 2008). The risk variant has since been linked to increased calorie and fat intake (Qi *et al*., 2008) and increased BMI in children, consistent with early-onset obesity, which is induced due to mutations in MC4R (Farooqi *et al*., 2003). Several additional loci near or in BDNF, GNPDA2, KCTD15, ETV5, MTCH2, TMEM18, NEGR1, and SH2B1 genes in the associated regions are highly expressive or known to act in the central nervous system (CNS) can cause the rare monogenic forms of obesity and having a role of CNS pathways in predisposition to overall obesity studied from the GIANT (Genetic Investigation of Anthropometric Traits) international consortium (Willer *et al*., 2009) and the deCODE Genetics group (Thorleifsson *et al*., 2009).

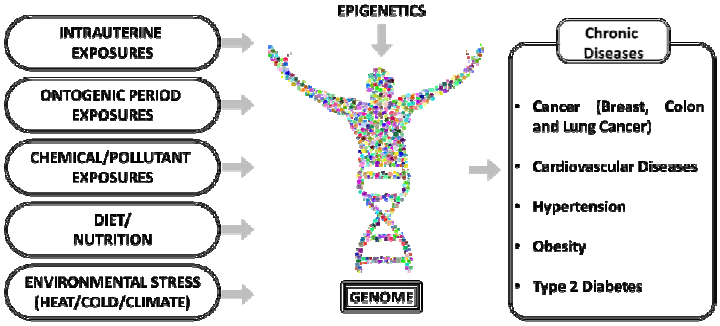

Fig. 5. Environment role in Epigenetics modifications causing some chronicdiseases.

There are more than 40 genetic variations linked to obesity and fat distribution that have been studied. However, these variants have a role in obesity, but it does not entirely explain the heredity of obesity because some epigenetic marker's role must govern this obesity phenomenon. Since Epigenetic modification and Genetic markers directly affect the sequence-specific interactions between DNA and proteins, this explains that genetic and epigenetic factors are closely interlinked (Ptashne *et al*., 2010). Based on extensive human epidemiologic data studies, early environmental influence had a significant impact on the epigenetic variation in childhood. For instance, a survey tells that mothers tend to have an obese child if they had an obesity and hypertension problem when they are pregnant, which later on permanently affects the metabolism of their upcoming child and risk for developing chronic disease in later stages of their life (Dabelea *et al*., 2008). The term metabolic imprinting was proposed to describe a subset of adaptive responses to early nutrition characterized by susceptibility confined to a critical ontogenic period and a long-lasting influence into adulthood (Waterland and Garza, 1999). Such as, due to a lack of dietary methyl donors, specific methylation abnormalities may occur during fetal development (Waterland and Michels, 2007; Poirier, 2002; Biniszkiewicz *et al*., 2002). The increased fat mass associated with the FTO gene variation is caused by a change in FTO demethylase activity, which can be linked to increased food consumption, decreased energy expenditure, or both. Numerous different environmental and epigenetic mechanisms mediate the genes expression linked to increased adiposity and BMI, such as the MC4R gene, which has its methylation reduced after it is exposed to a high-fat diet for a long duration (Widiker *et al*., 2010), the Peroxisome proliferator-activated receptor gamma (PPARγ), a protein which interacts with histone acetyltransferases (Choy *et al*., 2010) during adipogenesis add on the effect of diet on methylation of Pro-opiomelanocortin (POMC) (Plagemann *et al*., 2009) and Leptin (Milagro *et al*., 2009), which causes severe obesity that begins at an early age. Hence, epigenetic regulation is strongly linked to the genetic markers for causing obesity.

Genetic and epigenetic marker role in Type 2 Diabetes. Diabetes is a disease affecting millions of lives worldwide, and according to WHO records, there have been 1.5 million deaths in the year 2019 due to it. Diabetes mellitus is a chronic disease caused by a hereditary and acquired deficiency in insulin synthesis by islets of Beta cells in the pancreas or by the ineffectiveness of the insulin produced by it. Such a deficiency causes elevated glucose concentrations in the blood, damaging many of the body's systems, including the blood vessels and nerves (WHO, 2021). It happens due to the low production of the insulin hormone, also known as Type 1 Diabetes (T1D), or the body does not utilize it effectively, known as Type 2 Diabetes (T2D). According to the National Institute of Diabetes and Digestive and Kidney Diseases, T2D is the most prevalent kind of diabetes, and it has a strong correlation to obesity. It is accounted for almost 90% of all diabetes cases worldwide. T2D occurs most frequently in adults, but it is becoming more common in adolescents (amritamedicalsite, 2021). Mutations in the MC4R gene [The melanocortin-4 receptor gene, controls body weight, MC4R protein produced by hypothalamus] and Transcription factor 7-like 2 [(TCF7L2) gene, regulates glucose tolerance of the body] are suspected to be related to T2D (Duval *et al*., 2000). TCF7L2 is one of the highly conserved domains which encodes for functional domains, making it an integral part of the Wnt pathway involved in developmental biology (Del Bosque-Plata *et al*., 2021). It has been found in a study that when palmitate (a fatty acid) is exposed to human pancreatic islets, it induces a group of global and specific DNA methylation

alterations followed by the reduced mRNA expression and decreased secretion of insulin (Hall *et al*., 2014). In other words, the study demonstrated the role of environmental factors such as obesity in increasing the methylation status of the adiponectin gene promoter, producing adiponectin factor [one of the adipokines] responsible for controlling insulin sensitivity of the cells. (Kim *et al*., 2015). In obese individuals, epigenetic activities like high exposure of palmitate to islets of the pancreas alter the methylation in a way that activation of DNA methyltransferase-1 takes place, and a specific region (promoter) of adiponectin gene is hypermethylated, which leads to the low expression level of the gene that ultimately reduces the insulin sensitivity of the body cells and hence glucose components remain unabsorbed by them. The confirmed gene loci of plasma adiponectin concentration (rs17300539 and rs266729) were found to be present in the CpG island of the adiponectin promoter, and as a result, the CpG sites can either be introduced or removed, in accordance to the genotype (termed CpG-single nucleotide polymorphism (SNP)). Talking about another adipokine gene, the resistin gene [RETN], its promoter region is shown to have reduced methylation of cg02346997 [DNA methylation site] present in the RETN promoter (Nakatochi *et al.*, 2015). Hence, there is an epigenetic role occurring in regulating the adiponectin gene. In addition, DNA sequence mutations like structural variation, CpG SNP, and gene-gene interactions also play a significant role in epigenetic regulation. This may explain another critical part of the variation in susceptibility to type 2 diabetes. Several mechanisms are there to explain type 2 Diabetes which include altered epigenetic modifications in pancreatic β-cells44 (Park *et al*., 2008) and decreased mitochondrial DNA content (Kwak and Park, 2016).

Environmental factors like obesity, age, diet, and physical activity regulate epigenetic regulations. For example, Suppose adults are prone to Intrauterine exposure to hyperglycemia. In that case, the probability of occurrence of diabetes and obesity can be seen in offspring's, explained in a study performed on Pima-Indian families. Their study found the relationship between the mothers and its effect on offspring when she is conceived after being diagnosed with type 2 diabetes. Their result showed that the offspring had higher chances of being overweight and developing type 2 diabetes in the future than their sibling who were conceived before their mothers developed the T2D disease (Dabelea *et al*., 2000). Another study on the Arabs population correlates BMI and T2D with changes in offsprings epigenome. EWAS [Epigenome Wide Association Studies] was conducted, and it was found that BMI is highly linked with methylation of SBNO2, LY6G6E SOCS3, CPT1A, SREBF1, and PRR5L gene, and T2D was found to link with TXNIP (Al Muftah *et al*., 2016). TXNIP (thioredoxin-interacting protein) gene encodes for a protein that interacts with thioredoxin antioxidant and brings about its inhibition. It also contributes in regulating glucose by reducing the insulin sensitivity of the peripheral cells of the body [skeletal muscles in T2D patients] by causing the apoptosis of pancreatic beta islets cells [pro-apoptotic beta-cell factor] so that no more insulin can be made freely available for the body cells, hence reducing insulin sensitivity (Parikh *et al*., 2007). This is an indirect way to reduce the insulin sensitivity of the cells. Here methylation plays a positive role in glucose regulation, unlike other cases that we have read about in this study. This is mainly done by methylating the TXNIP gene, thereby inhibiting the production of TXNIP protein so that no more apoptosis of beta cells could occur and ideal insulin production can be achieved. Arabs population study found that individuals diagnosed with T2D showed less methylation of TXNIP, resulting in the higher TXNIP expression and, hence, lower insulin expression (Al Muftah *et al*., 2016). Accordingly, we can say that both genetic and epigenetic factors are responsible for causing diabetes.

Role of the genetic and epigenetic marker in cancer. Cancer is the sign of epigenetic and genetic modifications (Ducasse and Brown, 2006; Aguirre-Ghiso, 2007; Esteller, 2008; Baba *et al*., 2009; Ellis *et al*., 2009). Numerous studies have actively participated in characterizing the genomic landscape of cancers from mutation spectrum in different cancer subtypes to oncogene-driven signalling pathways (Lu *et al*., 2020). Cancer cells are freed from many of the limitations that normal cells are subjected to as a result of genetic alterations. Normal cells do not divide unless the body's homeostatic machinery stimulates them; they also do not survive irreparable harm. They do not wander away from tissue to start new colonies forming in other body parts. The majority of cancer cells, on the other hand, have lost all of the regulatory factors that safeguard the body from chaos and self-destruction. Cancer cells primarily grow uncontrollably, resulting in malignant tumours formation that invades healthy tissue (Iwasa *et al*., 2016). Genes involved in carcinogenesis are divided into two broad categories: tumor-suppressor genes and oncogenes. Tumor suppressor genes are like the brakes on a cell; they encode proteins that restrain cell growth and prevent cancer. On the other hand, oncogenes are genes that code for proteins that facilitate the loss of growth control and turn a cell into a malignant state. Oncogenes can cause genetic instability, prevent a cell from dying, or promote metastasis (Iwasa *et al*., 2016).

Over the last several decades, there has been a focus on the genetic basis of cancer, specifically on the mutational activation of oncogenes or the inactivation of tumour suppressor genes. But, since the mid-1990s, a large body of evidence has accumulated suggesting that heritable changes governed by epigenetic modifications might be critical for all types of human cancer (Jones and Laird, 1999; Jones and Baylin, 2002; Herman and Baylin, 2003). These findings, especially chromatin and DNA methylation patterns that are foundationally modified in malignancies, have paved the way for new cancer research, prevention, detection, and treatment approaches. Several well-known epigenetic alterations have been associated with altered gene expression

patterns and abnormal gene functions, which are essential in cancer pathobiology (Kanwal and Gupta, 2010). The epigenetic pathway to cancer is dictated by chromatin's structure, which includes histone variants and modifications, DNA methylation, nucleosome remodelling, and some small non-coding regulatory RNAs (Sharma *et al*., 2010). Tumor suppressor genes such as O6-methylguanine-DNA methyltransferase (MGMT), which encodes a DNA repair gene, CDKN2B, encoding for a cell cycle regulator p15, and gene RASSF1A, encoding a protein that interacts with the oncogene RAS, have all been linked to perform a protective role against tumorigenesis (You and Jones, 2012). Cancers typically show promoter hypermethylation of classic tumour suppressor genes, which cancer cells exploit for tumorigenesis (Baylin and Jones, 2011).

Cancer is caused by a combination of accumulative genetic mutations, epigenetic alterations, and environmental influences (Lu *et al*., 2020). The direct evidence for close epigenetic-genetic cooperation is observable in the colon cancer cell line HCT116, in which one allele of CDKN2A (Cyclin-dependent kinase inhibitor 2A) and MLH1 (MutL homolog1) is silenced by DNA. In contrast, the other allele is genetically mutated by methylation (Baylin and Ohm, 2006). The mismatch-repair gene MLH1 plays a vital role inthe stability of the genome, and the loss of function of this gene by promoter hypermethylation causes microsatellite instability (Krivtsov and Armstrong, 2007), and CDKN2A is a tumour suppressor gene that encodes the p16-INK4a protein which is involved in cell cycle progression, differentiation, senescence, and apoptosis (Jiao *et al*., 2018). Proteins in the methyl-CpG-binding domain (MBD) family are the primary candidates for DNA methylation readout because they recruit chromatin remodelers, histone deacetylases, and methylases to methylated DNA associated with gene repression (Du *et al*., 2015). Methyl-binding domain (MBD) proteins, including MBD1, MBD4, MBD2, MeCP2, bind to methylated CpG sites, and MBD2 and MBD1 genetic mutations increase the risk of breast and lung cancer, respectively (Sansom *et al*., 2007). So, even though acquired genetic changes are the primary cause of cancer initiation and progression, it is evident that microenvironment-mediated epigenetic alterations have a crucial role in neoplastic progression (Herceg, 2007).

Therapeutic potential of epigenetic interventions. The results of decades of epigenetics research have finally made their way into medical practices. Clinical trials are underway for many drugs and tests based on epigenetic modifications and regulators, and some have already been approved for regular use. There are two possible methods for reversing the epigenetic changes in cancerous and other abnormal cells. The first targets the abnormal epigenetic regulators that are ultimately responsible for the changes, while the second is to erase and overwrite the modification patterns. Much of the research in this field has focused on anti-cancer drugs that can reverse the abnormal epigenetic modification patterns found in cancer cells (Ennis and Pugh, 2017). On the contrary, much of the potential of epigenetic therapies for non-cancerous diseases is still restricted to the labs, or more accurately, in the early stages of clinical trials (Mau and Yung, 2014).

Although some epigenetic medicines are in use and many more are on the way, histone-modifying drugs, particularly HDAC inhibitors, have likely attained significant clinical attention. For example, the Food and Drug Administration (FDA) has approved Vorinostat to treat patients with cutaneous T-cell lymphoma (Tollefsbol *et al*., 2010). HDAC and HATs play an essential role in gene regulation. In general, HATs promote transcription in the affected chromosomal regions, while the function of HDACs is to reverse the acetylation of histone, which condenses chromosomal DNA and leads to a reduction in transcription (Mottet and Castronovo, 2008). HDACs have also been discovered to directly modify a wide range of non-histone substrates, including pRB, p53, and E2F-1, Ku70 (Marzio *et al*., 2000; Chan *et al*., 2001; Kawaguchi *et al*., 2003; Chen *et al*., 2007). Many other drugs are in clinical trials that have the potential to normalize aberrations not only in DNA methylation but also in histone modifications catalyzed by DNMTs (Tollefsbol *et al*., 2010). Until now, the DNMT inhibitors 5-aza-20-deoxycytidine and 5-azacytidine for the treatment of myelodysplastic syndrome (MDS) and the HDAC inhibitors, Panobinostat- for the treatment of Multiple myeloma; Romidepsin and Vorinostat- for the treating Cutaneous T-cell lymphoma (CTCL); Belinostat and Chidamide- for the treatment of Peripheral T-cell lymphoma (PTCL) have been approved by the FDA (Cheng *et al*., 2019). Nicotinamide and Trichostatin A (TSA), both HDAC inhibitors, were used separately to decrease Tumor Necrosis Factor (TNF), which consequently reduced IL-6 expression in macrophages isolated from Rheumatoid arthritis patients' peripheral blood mononuclear cells (PBMCs) (Gillespie *et al*., 2012). Recently, for Multiple Sclerosis (MS) and other inflammatory diseases, the drug Citrullination has been proposed to target epigenetic intervention related to this disease. Citrullination asserts that shielding citrullinated histone epitopes, that perform a crucial role in neutrophil extracellular trap (NET) formation and can assist in preventing the intensification of the inflammatory response in MS other inflammatory diseases (Chirivi *et al*., 2013). Obesity and T2D, which are caused due to BCL11A gene (male-specific association), global DNA hypermethylation (diabetic retinopathy), HIF3A gene locus methylation epigenetic errors, can be cured through the prenatal diets (consists of the optimum amount of vitamin folic acid, vitamins B2, choline, methionine, B6, betaine, B12) (Vickers *et al*., 2000; Dick *et al*., 2014; Mau and Yung, 2014).

The main challenge in using epigenetics in therapy has been finding high-specificity biomarkers and designing therapeutics targeting these specific markers. It is not always clear whether certain illness linked to epigenetic modification is the cause of that disease or, due to the

result of that disease, epigenetic modification occurs (Mau and Yung, 2014). Moreover, epigenetic regulators used in therapy affect more than just the target of interest. They also affect the neighbouring areas and have dose-limiting toxicities (Gray and De Meyts, 2005). Recently, more potent data sets can help to distinguish non-Mendelian inheritance patterns, which are now being expanded and studied by the epigenome GWAS (Best and Carey, 2010).

Prospect of Epigenetics in ImprovingBioethanol Production. As we already described some chronic diseases related to genetics and epigenetics interlink phenomenon and development of epigenome as new approach for medical practice, we also want to introduce its role in industrial perspective, such as high-efficiency production of bioethanol. Over the past few years, out of all the petroleum fuels, petrol has been proved as a major source of environmental pollution as it undergoes the process of incomplete combustion, mainly because of the unavailability of sufficient oxidants (Bušić *et al*., 2018; European Biomass Industry Association [EUBIA], 2022). Sometimes, preferable oxidants of "high octane number" are added to petrol, but this methodology has failed. There comes the role of Bio-Ethanol in the market. "Bio" means anything that is extracted from biotic components and is biodegradable (eco-friendly) in nature. A deficient proportion of smoke is produced when mixed with petrol because of the high octane index and complete combustion. If we prefer bioethanol over regular fuels, then there is no need to burn the crops consumed during production (Tse *et al*., 2021).

It is mainly derived from the fermentation of sugars present in the leftovers of crops like sugarcane and corn. They have been the upfront source of bioethanol since the late 1970s. The latest interest lies in bioethanol production from lignocellulosic biomass (Chin and H'ng, 2013; Sahay *et al*., 2021). Such lignocellulosic biomass includes maize straws and wheat, corn starch, and sugarcane bagasse (Ghosh and Das, 2020). It comprises polysaccharides like cellulose, hemicellulose, pectin, lignin, and a minimal quantity of proteins, minerals, and phenolic compounds. Unlike cellulosic biomass, lignocellulosic biomass requires rigorous pre-treatment because of its rigid lignin content. Hydrolysis is the process of breaking down complex sugars like hemicellulose and cellulose into corresponding simple pentose and hexose carbohydrate units like glucose and xylose with the aid of industrially capable biofuel producing microorganisms. It has been observed that some potential biomass crops contain secondary metabolites that are toxic to these microbes or the degrading enzymes produced by them (Sengupta *et al*., 2020). Sometimes, acid pre-treatment also produces dehydrated sugars that are toxic to these microorganisms (Ghosh *et al*., 2020).

There is a method to modulate and alter the genes responsible for the production of xylose degradation enzymes to obtain the enhanced quantitative output of ethanol. It is achieved by genetic engineering, gene deletion, promoter engineering, direct evolution, and epigenetic engineering (Adebami and Adebayo-Tayo, 2020). For genetic engineering manipulation of the microbe to produce enough amount of enzymes, one should have the complete knowledge of concepts of genomics, the whole sequence of the human genome, gene sequencing techniques, and the entire set of functioning of the engineered microbial strain to accurately target the sites for genetic alterations (Adebami and Adebayo-Tayo, 2020). But in the case of epigenetic engineering approaches, no disturbance with the genome is needed; instead, these are changes in the gene sequences that are heritable, ultimately changing the physiological appearance of an organism without interfering with the DNA sequences (Adebami and Adebayo-Tayo, 2020). A Genome sequencing study on *Trichoderma reesei,* a cellulase producing industrially beneficial fungus, has showcased that the genes coding for various hemicellulases, cellulases, and auxiliary activities are clustered together (Aghcheh and Kubicek, 2015). The functional analysis of the *Trichoderma reesei* laeAsub type lae1 [**(loss of aflR expression A), aflR regulates transcriptional activation, laeA gene deactivates aflR gene]** has shown a significant amount of increased production of cellulase due to overexpression of lae1. H3K4 **(H3 histone unit on 4th lysine amino acid [K for lysine])** is an epigenetic modification associated with the H3 histone of the chromatin complex. In *Magnaporthe oryzae,* H3K4 is methylated by the MOSET1 gene (a gene for methyltransferase in Magnaporthe oryzae, a fungal organism) encodes the methyltransferase enzyme to transfer methyl groups to H3K4. Thereby reducing the induction of cellulase. Also, the nucleosome presents in the promoter of the genes producing two major cellulases, CEL7A and CEL6A **(cellulases enzymes for cellulose degradation)** of *Trichoderma reesei* rearranges itself, and the rearrangement has also been analyzed (Zeilinger *et al*., 2003). It has been found that this promoter nucleosome which is usually present downstream to the motif sequence that binds with the transcriptional activator, was lost. Hence, ultimately TATA box and promoter were made accessible for the RNA polymerase to express transcriptional unit and produce CEL7A and CEL6A. Interestingly, overexpression of yet another GCN5-N-acetyltransferase **(General control non-depressible 5, an acetyltransferases enzyme)** from *Trichoderma* reesei causes a double enhancement of cellulase formation (Häkkinen *et al*., 2014). In a nutshell, either the microorganisms producing degrading enzymes should be resistant enough against secondary metabolites and toxic compounds (Genetic Engineering approach), or the degrading enzymes that they produce should be sufficient enough to neglect the need of genetically modifying microorganisms and out casting the need of purchasing costly enzymes (Epigenetic Engineering approach).

FUTURE SCOPE

The continuous progress in molecular biology research shows the relation of environment impact on our gene

regulation activity which regulates the organisms phenotype. The epigenome involvesnumerous molecular constituents like DNA methylation, non-coding RNAs, histone proteins, and their post-translational modifications. In Epigenetic mechanisms, each and every aspect of gene expression gets influenced, from gene accessibility in the chromosomal pool to post-transcriptional and transcriptional RNA modification and translation. Till date, broad spectrum of molecular players has been discovered as well as their role, involvement, and the variety of mechanisms involved, indicates that even seemingly simple metabolic pathways of gene regulation may show dynamic and complex operations. Therefore, for managing disease and to cure, it has become essential to understand the genetic and epigenetic roots of disease. Different chronic diseases are speculated to arise from genetic factors/markers interacting with or getting affected by either beneficial or harmful environmental agents. This background biological understanding of epigenetics involvement and its interaction with genetic markers enables us to understand the contribution of genetics and epigenetics in the development/research of individualized genomic and epigenomic profiling. Thus, leading forward in the direction to the creation of epigenetically inspired medicinal era/personalized medicine for diagnosing and treating a wide array of chronic diseases. Significant research is currently using an epigenetic modification to improve production of various bioengineered products such as bioethanol as well as in treating the different chronic disease. Moreover, it opens the path for exploration of different endeavor and prospects for deep and better understanding of changes occurring at gene level.

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