Page 268 to 285

Volume 1 • Issue 5 • 2017

Research Article

Chronicles of Pharmaceutical Science

ISSN: 2572-7761

Epigenetics and It's Effect In Human

Jayita Goswami*

Independent Researcher

***Corresponding Author:** Jayita Goswami, Independent Researcher USA.

Received: September 19, 2017; **Published:** September 26, 2017

Abstract

In 1940 Sir Conrad Waddington first described the Epigenetics as a branch of Biology. Effect of genes and its modification is well known for decades. Various effect of epigenetics is the recent development. Recent scientific evidence proved that not only sequence of DNA is responsible for change but other molecules in a cell can bring phenotypical change or can cause diseases. DNA methylation, histone modification, acetylation are the reasons of epigenetics. Some of these changes are heritable. Methylated DNA or gene produces miRNA and silences gene. mi RNA is a noncoding RNA.

These changes have observed in human, animals and in plants. Methylation down regulate genes followed by phenotypical changes appear. Food, environment, chemicals are the reasons of methylation. Several human diseases have the profound connection with epigenetics. Current research targeting histone remodeling techniques or drugs that target histones.

Every single biochemical reactions in the living organism is energy driven. The smallest battery in the world is mitochondria. Mitochondrial dysfunction creates several serious diseases. And some of the diseases are interlinked. It can be considered as conservation of mass and energy in the cell. Perturbation of energy level creates various dysfunction in the cells. Cells follow laws of thermodynamics. Epigenetic related diseases and drugs are under trial, especially cancer and Alzheimer's drugs. Still more research needs to be done to confirm that whether epigenetics is always the reason for mutation.

Abbreviation: DNA: Deoxy ribonucleic acid; RNA: Ribonucleic acid; ROS: Reactive oxygen species; PCR: Polymerase chain reaction; CDC: Center of disease control; PTSD: Post traumatic stress disorder; SOD: Sodium dismutase; RAS: Renin angiotensin system

Volume 1 Issue 5 September 2017

© All Copy Rights are Reserved by Jayita Goswami.

Introduction

Epigenetics is a fascinating topic in the world of genetics. It can be due to physiological, pathological or environmental. DNA modulation takes place by histones. Methylation and acetylation of histones, generally in lysine amino acid can change the DNA or gene's activity. DNA methylation takes place in the architecture of cell's nucleus. The agents that modify genes can be from the environment or from food. Carbonyl compound, Chloro-Fluro carbon from the toxic air and some chemicals mimic DNA bases can cause the genes acts differently. Acetylation occurs in active chromatin.

Citation: Jayita Goswami. "Epigenetics and It's Effect In Human". *Chronicles of Pharmaceutical Science* 1.5 (2017): 268-285.

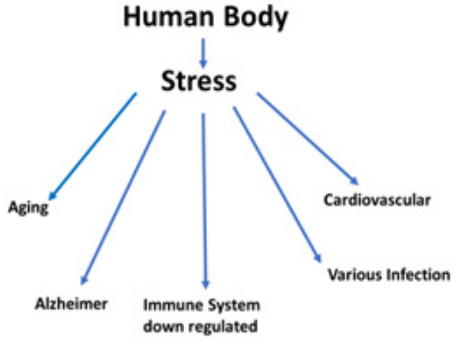
Deacetylation takes place in heterochromatin; whereas methylation takes place in the active and inactive region of chromatin. Methyl group gets attached to cytosine and guanine bases. Inactivation of X-chromosome due to methylation of histones causes x-linked diseases. Fragile x chromosome is the reason behind several mental retardations. DNA methylation creates cancer in the human. Gene instability is also related to mental disorders. Gene can be silenced through RNA, antisense transcripts, noncoding RNA etc. Micro RNA (miRNA) causes silencing of genes. They are 22 nucleotides long and attach at 3' UTR of coding RNA and make it noncoding. Changes in the promoter region of the gene causes the big effect. Accumulation of CGGs or CpG in promoter region creates epigenetic change [1-5]. Epigenetic change takes place from germ line to mature cells.

Athletes who are involved with extreme sports produces atomic oxygen that can change the DNA's electronic state, it is called epigenetic change. Histones acts like a the belt around DNA sequence. Changes in histone is post translational and it changes the DNA packaging. Modification of DNA structure causes the change in transcription factor docking site. Some research group defined epigenetics as the change in gene expression and activity without changing DNA sequence. DNA methylation established by three methyl transferases such as DNMT1, DNMT3a, DNMT3b that catalyzes the transfer of methyl group S-adenosine-L methionine to cytosine bases. This methylation is restricted in most mammals.

One of the main function of histone modification is to change the chromatin structure i.e. euchromatin. Euchromatin is less condensed and accessible for change by the transcription factors. Modification found in at least 60 histone residues, and they are as much as eight different types. Acetylation, methylation, ubiquitination, phosphorylation is the most prominent one. Acetylation takes place by histone acetylation transferase which is a part of gene transcription.

Various diseases caused by epigenetics such as heart disease, obesity, various cancer, autism, fragile x chromosome, ATR x syndrome, Angelman syndrome, Prader-willy syndrome, Coffin Lowry syndrome etc. Recent research evidence shows that excess iron in water creates free radicals in the body that harm neuron cells and causes Alzheimer. X mental retardation gene FMR1 located in X chromosome. Generally, healthy gene contains 44 repetitions of CGG whereas diseased person gets 200 repetitions. It causes methylation in the promoter region and it shuts down FMR1 gene. The repetition of CGG causes the DNA sequence fragile it called fragile X chromosome.

Nicotine, alcohol, some chemicals like asbestos, bisphenol can interfere with chemical reaction in the body. Resveratrol, vitamins like B12 and folic acid protects the body from chromosomal changes. This is the positive effect of epigenetics. Diet is very important in human or animal body. Food is the building block of DNA, proteins, cells, tissues etc. Lack of calcium causes bone loss or bone malformation. Low level of folic acid in the body creates fertility problem i.e. immature egg, mobility, and lodging of eggs. It has found that maternal diet changes a lot of phenotypical character in offspring such as increased body mass, resistance against insulin, elevated blood pressure, altered immune system and response against antigens.



Diabetes and Obesity

Type two diabetes can be developed by epigenetic changes. Sometimes Type Two diabetes called as type M i.e. metabolic disorder. Excess carbohydrate uptake can activate trehalase type genes. It has already established that diabetes is controlled by several genes. People found success with mRNA inactivation techniques. Women with high triglyceride have the tendency to develop gestational diabetes during the third trimester of pregnancy. The child in the womb gets bigger in size and develops diabetic tendency in later life. High protein uptake controls blood glucose level. In addition to DNA methylation and histone modification, smoking, drinking, pesticides, and heavy metal can trigger alternative biosynthetic pathway followed by the change in chromatin structure and gene inactivation. Some vitamin deficiency e.g. folate and methionine can create diabetes as well. As we know any biosynthetic pathway is controlled by some precursors, some intermediate enzymes, and it produce by a cyclic reactions. Disruption in one path can cause change in others. Age is also the reasons for Type Two diabetes. Aging cells have fewer mitochondria or cells can suffer from oxidative stress due to dysfunctional mitochondria. Less exercise, less oxygenated place is also down regulate mitochondria. Hyperglycemia changes the chromatin structure in cells eventually it effects the genes.

Nuclear factor kappa light chain enhancer (NF-κB) in activated B cells controls DNA transcription, which is a protein complex and controls the gene that is related to inflammation and atherosclerosis. When people suffer for a long time with hyperglycemia eventually gets an ischemic heart, kidney failure, and skin infections. Abnormal level of insulin creates digestive problem and abnormal bowl movement.

P300 a transcriptional coactivator with histone acetyl transferase activity controls the glucose induced activation of transcription factors. Histone H2AX phosphorylation and lysine acetylation take place in higher level of glucose. High glucose concentration can overexpress p300 and mRNA level, and it binds to ET1 and FN1 promoter binding site. Small interfering RNA(siRNA) blocker or the chemical blocker like curcumin blocks p300 over expression. Prolong hyperglycemia causes tissue damage. P300 controls expression of multiple transcriptional factors and mRNA expression; it can be a target for therapeutic purposes. Mitochondrial dysfunction also observed in diabetes [6-11].

Cancer

Some cancers develop from gene methylation. Gene or DNA methylation causes the change in chromatin's structure [12-26]. Experimental data already established that epigenetic effect such as environment and food causes cancer in some part of the body. Chemicals that mimic DNA bases get incorporated into DNA sequence. It causes a change in the three-dimensional structure of DNA molecules. DNA gets fragile and mutation take place. Animal study shows that high-fat diet in the pregnant mother can give offspring's cancer in later life. Too much epigenetic influence activates oncogene and suppresses genes that control cancer.

Microbial proteins can dock in essential proteins binding site and make it unavailable for reaction. Current research trend suggest that prolong viral or bacterial infection in the body can give rise to cancer. Especially lymphoma has a direct relation with infection and cancer. Methylation, histone modification, and abnormal nucleosome positioning create cancer. The immune system, infection, and cancer is correlated to each other. Prolong diabetes is also the reason for cancer development. Diabetes is a disease that is related to the metabolic disorder, insulin production, heart disease, boil movement etc. Altogether it can develop cancer.

In third world country, where plant fertilizer and insecticides get used in a large amount, eventually, it enters in the food chain and can cause cancer. If industrial waste is not controlled properly, it pollutes the soil and waterbody. Heavy metal, and arsenic pollutes water that can give rise to an ulcer in the stomach followed by cancer. Viruses are historic particle they exist on earth for a long time. Viral sequences are incorporated in human genome quite a bit. Highly polluted air and Epstein Barr virus causes nasopharyngeal carcinoma or lung cancer. DNA virus like adenovirus and RNA virus like hepatitis C can cause cancer. Almost 15% of human cancer develops due to prolong viral infection. Some researchers used the virus as a medicine for breast cancer and liver cancer. Protein coagulation, blood cell coagulation occurs due to bacterial or viral infection. It triggers cancer development. Tumor development can produce blood coagulation. A blood clot is an early indicator of cancer formation in human body.

Oxidative damage breaks chromosome and creates sticky ends followed by unequal cell or chromosome division. For abnormal cell and chromosomal division aneuploidy or polyploidy takes place or some essential genes can be lost through the process. Epigenetics causes a change in DNA sequence that's call mutation. One amino acid change causes point mutation that occurs very often. More than one amino acid change can cause frame shift mutation, and most of the time it is visible through phenotypical or genetypical change.

It is already estrablished that cancer can develop becasue of DNA methylation. Age related methylation is also the reason for older age cancer. Here mitochondrial dysfunction takes place. Multiple promoter related CpG island methylations are observed in various cancers, with age this methylation also increases. Tumor suppressor gene TWIST2, MLH1, BRCA1 gets highly methylated and loses it's activity due to methylation. Percent of gene methylation varies between breast cancer subtypes. APC, DLEC1, GRIN2B, GSTB1, HOXA1, HOXA10 etc. genes are related to breast cancer subtypes.

With high resolution flouorescent imaging, it has observed that seven different carbohydrates are present in cancer cell membrane compare to normal cells. These carbohydrate can also be a target for biomarker or for drugs. Sialic acid also found in large cluster of cancer cells. Sialic acid is present in across the animal kingdom. It is present in large amount in brain cells as well. Sialic acid present in Plants, Fungi, Yeast, Bacteria's, Drosophilla and in other insects. Sialic acid takes place in nural transmission in human. This acid takes part in cell recognition, cellular attachment, and cell signaling. Sialic acid also helps with cancer metastasis.

Cardiovascular

Stress has immense effect in the cardiovascular system. Stressful life creates abnormal life style i.e. people eat unhealthy food, exercise less. It creates lipid or fat accumulation in the arteries. Heart put extra effort to pump blood all over the body. Sometimes narrow vein and arteries get clogged or the valves remain open; oxygenated and deoxygenated blood get mixed. When people carry heavyweight regularly, they have a tendency to build thicker heart wall. Through body's natural protective mechanism heart creates an extra layer in the outer wall of the heart; which eventually affects heart's natural activity i.e. blood pumping and breathing. Being over-weight due to unhealthy food and lifestyle can cause the cardiovascular disease. Poor hygiene in mouth builds bacterial pluck in the artery as well as in heart, and eventually it can cause heart attack. The people pursue extreme sports they can get heart attack too. During exercise, body needs plenty of oxygen. Lack oxygen can create local paralysis. Extreme sports player gets deep vein thrombosis which can be treated with anticoagulant medicine. Heart disease is the number one killer in the world, Especially, women are the victims of heart disease. One out of three women dies from heart disease. Peripheral leukocytes are the marker of cardiovascular disease and artherosclerosis. High leukocyte count shows the threat of heart disease in human [27-30]. These are all epigenetic influence that give rise to cardiovascular disease without changing DNA sequence.

Hypertension

Stress is an inevitable part of our lives. Living under stress for long time eventually creates hypertension and other abnormalities in the body, such as stroke, kidney disease and myocardial infraction. Hypertension affects central nervous system too. DNA methylation, post translational histone modification, and mRNA modification are the epigenetic reasons for hypertension. Long term Pulmonary hypertension creates paralysis in long run. Inflamed artery get swelling inside the artery wall. It blocks oxygenated blood flow in the cells. Cells suffer from oxygen followed by paralysis. It has found that hypertension, inflammation and abdominal obesity are inter-linked. Long time hypertension can give a cerebral attack.

Central nervous system gets effected because of hypertension. It also occurs due to high blood sugar or diabetes. Hypertension, diabetes and ischemic heart are related to each other. High sodium and low potassium in food, fewer vegetables in diet can give hypertension. High alcohol consumption also causes high blood pressure. High sugar, high fat or trans-fat, red meat is the epigenetic reason for high blood pressure. DNA methylation at CpG island and histone acetylation pathways are the epigenetic effects for hypertension. It limits nephron development. RAS is a hormonal system that controls sodium and water level in plasma and arterial blood pressure. Maternal water deprivation and protein deprivation during pregnancy causes renin angiotensin system (RAS) over expression in off springs.

Hypertension is the reason of heart and kidney failure. The level of aldosterone in blood varies according to dietary sodium uptake. Aldosterone is a steroid hormone and produces from zona glomerular or adrenal gland. It controls Na^+ uptake and Ka^+ excretion combined with RAS. Oxidative stress and inflammation causes vascular endothelial cell's stiffness, followed by the narrow vascular wall. It creates extra pressure over blood flow [31- 33].

The recent evidence shows that immune system is related to hypertension. Activation of T cells including tumor necrosis factor alpha, interleukin 6 and interleukin 17 is related to hypertension. The central nervous system controls the immune cell activation. Over production of cytokines creates an imbalance in the body and followed by high blood pressure, heart and kidney damage, the stiffness of blood vessels etc. A certain type of B cells produces an excess number of antibodies under stressed or high salt uptake condition. Moderation in diets such as green vegetables, pigmented fruits and vitamin C can keep body healthy and free from methylation. Pigmented fruits have capability to absorb atomic oxygen that can reduce damaging particles in the body. Vitamin C helps with Ca+ uptake at the same time keeps blood thin. Abnormalities in the innate immune system, cholinergic, adrenergic, AT1 and toll like receptors are the points of interest in hypertension related immune system and development of drugs.

Alzheimer

DNA hypermethylation, histone deacetylation, and microRNA change are also the reason for Alzheimer's. β amyloid plaque in the brain causes brain malfunction [34-40]. Learning impairment and dementia is the hall mark of Alzheimer's. Methylation takes place in cytosine and which has guanine nearby, together it develops CpG cluster. Methylation takes place in mitochondrial and ribosomal DNA. Some researchers also thought that short peptides which block ribosomes can also be the reason for Alzheimer's. Immature peptides especially made with hydrophobic amino acids can form plucks.

All these phenomena is related to gene transcription. DNA methylation, histone modification, and posttranslational miRNA suppression take place due to epigenetics. Oxidative damage is the reason towards abnormal protein synthesis in the ribosome. mRNA and tRNA level goes down. Decreased level of tRNA was observed in the cerebellum. Oxidation of rRNA takes place. β amyloid plaque looks like the cluster of neurofibril and the tau protein attached to it. It causes synaptic dysfunction, and problem with neuronal connectivity.

These pluck are made of small peptides that look like small microtubules. Aβ is highly insoluble, it causes the death of brain cells. The death of brain cells causes dementia. This disease appears in older age. It can give the point of discussion that accumulation of epigenetic changes or methylation over the years turns into Alzheimer's in older age. It has observed *in vitro*, lower level proteome inhibition in the glia cells causes rRNA oxidation.

This type of scenario explains cross talk between protein synthesis and protein degradation. Mitochondrial malfunction is one of the reasons for Alzheimer's initiation. Mitochondrial displacement loop or D loop region and the genes MT- ND1 and MT- ND6 shows methylation and the possible pathogenesis for Alzheimer's. SOD (super oxide dismutase) gets down regulated followed by higher production of ROS takes place. It impairs electron transport chain in mitochondria. Excess Ca^{2+} uptake hampers buffering capacity and calcium channel's activity.

Dysfunctional mitochondria produce pro apoptotic proteins that trigger apoptosis amyloid cascade. Those proteins enter the nucleus and starts nuclear fragmentation. Lack of autophagy causes Aβ accumulation. Autophagy and lysosomal degradation procedure are dysfunctional in Alzheimer's disease. Autophagy generally clears bodies unwanted proteins and other bigger molecules. Lysosomal vesicle contains toxic hydrolases and it produces pro-apoptotic proteins that migrate to nucleus and breaks down nucleus at the same time, produces β amyloid proteins. β amyloid is not easily degradable. In high acidic condition, it degrades *in vitro*. Amyloid precursor protein metabolites and lysosomal dysfunction create amyloid pluck. The highly phosphorylated tau protein attaches with microtubules and creates the β amyloid cluster. Defective autophagy vesicles with large vacuoles eventually creates β amyloid pluck too.

Spingolipids and the side chain ciramides accumulates in mitochondria and it retards mitochondrial activity, certainly electron transfer chain. This thing happens due to hydrolysis of membrane spingomylinase. Chronic diseases and oxidative damage impairs

mitochondrial memebrane and it's activity. Neorodegenerative diseases are linked with mitochondrial dydfunction such as Alzheimers, Parkinsons, Huntingtons etc. Mitochondrial memebrane action potential is coupled with proton pump. Uptake of electron always releases a proton. Singolipid and ceramide forms channels in mitochondrial outer membrane and through that channel protein uptake takes place. Methylation of C1 hydroxyl group changes the conformation of the membrane.

Immune System

B cell and T cell maturity can be controlled by epigenetics too. Epigenetic effect helps in signal transduction. T cells can memorize or imprint signaling messages in daughter cells. Microbes derived metabolites causes histone deacetylase. Microbes can cause DNA methylation followed by epigenetic change. Polyphenol has an immense effect on immune system. It can scavenge ROS, reduce oxidative stress, thiol redox mediated signaling modulation.

The epigenetic modification takes place by CD^{4+}, CD^{8+} memory cells. PTSD (post traumatic stress disorder) has an impact in the immune system. PTSD dysregulates hypothalamic, pituitary and adrenal axis activities by controlling the gene expression level; especially the genes involved with neuronal and endocrine proteins. DNA methylation is the reason for lower level of neuronal gene expression in PTSD patients. Stress related down regulation of immune system makes the HPV virus more active in PTSD patients.

Systemic lupus erythematosus (SLE) is an autoimmune disease where body produces antibody that targets body's healthy tissues. Various outside inducers could be the reason for it's development. It causes inflammation and attacks joint, heart, lung, kidney tissues. Fatigue, hair loss, light sensitivity, pain are some of the symptoms of this disease. Procainamide and hydralazine induces T cell methylation and SLE like cellular symptoms. In SLE patients same type of DNA methylation and cellular function also observed. Histone modification and DNA metylation takes place in SLE.

Defectic genetic control, uncontrolled cytokine and coreceptors expression causes lupus like immune diseases. Epigenetic effect takes place when genes and promoter region gets methylated followed by control over transcription factors. Autoimmune disease happens when body loses it's tolerance to small antigens. SLE, rheumatoid arthritis, type 1 diabetes, systemic sclerosis and multiple sclerosis. Histone acetylation and phosphorylation is related to gene activation, whereas histone sumoylation contradicts acetylation and phosphoylation activities. Histones are made of amino acids and its side chains are positively charged, it get attached with negatively charged genomic DNA [41-54].

Effect of Atomic Oxygen in Enzymes and Cell Energetics

Hydrogenase attacks the iron core of enzyme. Superoxide dismutase (SOD) removes atomic oxygen and unnecessary electrons. Another enzyme, catalase protects the cells from oxidative damage. It converts hydrogen per oxide to water and oxygen. One catalase molecule converts hundreds of hydrogen peroxide molecules. It is available in the peroxisomes.

H_2O_2 + catalase = H_2O + O-

Peroxiredoxin acts as anti-oxidative protein (PRDX1) which protects chromosome telomeres from oxidative stress. Over the period telomere can be shorter and gets vulnerable to hydrogen per oxide or oxidative stress. Hydrogen peroxide produces atomic oxygen that is highly reactive and damaging without an acceptor molecule. Superoxide dismutase produces hydrogen peroxide which eventually gets reduced by glutathione transferase. When singlet state electron does not get an acceptor molecule, it breaks the bonds and enzymes dismantles. Due to excess negative energy, molecular oscillation in the surrounding cytoplasm also changes.

Cytoplasm contains Na^+, Ca^+, K^+, Mg^+ ions, sugar and amino acids. Diffusion induced energy transfer takes place in the cytoplasm. Cytoplasm contains 70-80% of water. And it already proved that water is a good conductor of the electron. If water molecules exists between a donor and acceptor molecules, water acts as an electron tunnel. Within protein molecule, water and hydrogen bond acts as a buffer at the same time controls electron flow. The distance between donor and acceptor molecule should be 2-6 Å apart.

During oxidative stress, cell produces a lot of atomic oxygen, whereas lack of acceptor molecules creates an electron pool that is highly damaging. Every time when electron transfers across the membrane it picks up a proton that get released on the other side of membrane. Oxidation and reduction takes place at the same time. Lack of acceptor molecule of electron creates a high energy reduced environment (ΔG), that repeals within the cell. Water is a good conductor of heat energy. Cytoplasm contains a big amount of water. Finally whole cells machinery collapses due to reduced environment in the cell.

The laws of thermodynamics applies in cellular activities too. The first law is the conservation of energy. The amount of energy is constant. It converts from one state to the other. Metabolic reactions are constant oxidation and reduction reactions. The electromotive force measure the ΔG of cells. It releases free energy in the form of H^+. The energy releases in the form of heat energy and measured by kilo calories. Irreversibility of heat energy can also be observed. Some heat dissipates from biological samples. This heat dissipation perturbs the first law, but that energy is available to the environment in another forms [55-60].

$H_2 + 2e- = H^+$

$C_6H_{12}O_6 \rightarrow 6CO_2 + 6H_2O$, Free energy (ΔH) = -673 Kcal/-2815.8 Kjul/mol

Autism

The autism is a disease mainly defind as problem with social interaction, communication impairment, or repetitive action and restricted interest. The reason for autism is histone methylation. Without changing DNA sequence phenotypical or genetical change is possible. Genome wide study revealed that several genes and chromosomes are involved with autism but people found significant epigenetic effect in autism disease.

Nutritional deficiencies, immune deficiency caused by toxic agents, or any pharmacological over dose can be the reasons for autism. Autism occurs due to excess stress in the body. When a mother is pregnant, the excess stress in her living environment causes autism. Or when a little child goes through a harsh abusive childhood, the child can develop autism in later age. Neuronal developmental disabilities also another big reason for autism. Hyperbaric oxygen, healthy nutrition, heavy metal detoxification and psychological treatment by doctors are the treatment for autism [61-63].

DNA methylation and dead of brain cells are also linked with epigenetics and autism. Not only DNA methylation but mitochondria also take a big part in haematopoetic stem cells. Cell metabolism linked with mitochondria. Any malfunction in one of cell suborganelle can make major changes. Mitochondria is a key regulator in several metabolic signaling pathways. Several knockout gene experiments prove its efficiency. Accumulation of unwanted metabolites triggers several epigenetic pathways, such as excess melanin formation. It also controls the growth and development of hematopoietic stem cell. It has reported that maternal grandmother's smoking can increase the chance of having autism up to 50%.

Aging

Oxidative stress, aging are also part of epigenetic change in human body. Oxidative stress and aging are interlinked. Due to atomic oxygen many essential enzymes get dismantled. Cell loses regular metabolic pathways. Aging is directly related to epigenetics. Diet habit, the environmental factor can make people age quickly. DNA methylation, replacement of canonical histone with histone variants, altered non-coding RNA expression takes place during aging. Heavy carbonated air can cause lung disease and aging process faster.

In alcoholic liver disease, lipid metabolic pathways, reactive oxygen species (ROS), immune system get affected by enzymes that are directly affected by ROS. The general human body is not used to with excess alcohol in the system. It damages cells, tissues eventually create cirrhosis and carcinoma. The factors of aging can come from various sources. The major source can be sun exposure and smoking. The diet, excise, medication can also influence the aging process. Mitochondrial dysfunction is one of the main reason of aging. Singlet state electrons are highly damaging for cells. When donor molecule cannot get an acceptor molecule to share electrons, eventually donor molecule gets damaged or dismantle, e.g. enzymes. That's how biosynthetic pathway or chain reaction in cells perturbs whole cellular machinary or activities.

Nutrition deficiency already known to cause aging. Vitamins are the precursors of several biosynthetic pathways. Through everyday's work people losses cells. Source of protein helps to build muscles. Some sources of food can cause DNA methylation. Essential minerals for cell comes from food, that helps the cells to maintain its turgidity and keep several ionic channels in its active condition e.g. potassium channel, calcium channel etc. Vitamin D is fat soluble. It helps to absorb several minerals. Calcium, magnesium, potassium, iron, zinc get absorbed in presence of vitamin D. Deficiency of vitamin D causes the problem in blood, bone gets fragile along with other symptoms [64-69].

Skin

Skin cancer, skin abnormalities arise due to epigenetics. Tropical area or hot areas where the sun is intense, ultra-violate light causes cancer or damage the upper surface of the skin. Too much sun exposure causes the formation of melanin pigment. Longer exposure to ultra violate light causes damage in the upper and middle epidermis, eventually, it forms cancer. Small puffy nodules with a shiny surface or some time scaly surface are the signs of skin cancer. Local irritation, redness is also the sign of skin cancer along with the color change.

Sometimes vitamin deficiencies also cause skin abnormalities; such as vitamin B_{12} deficiencies. Age related epigenetics change occurs in older age. Skin loses its turgidity, plasticity. It also loses a number of melanocytes, Langerhans cells, a certain type of collagen etc. Cell death and less thickness in epidermis also take place. DNA methylation, and histone modification are the reason for epigenetic skin modulation. Food uptake and metabolic condition of a human are responsible for the epigenetic change. Some researchers mentioned that hypermethylation is high in the epidermis than dermis area.

Psoriasis is a skin disease that is associated with the immune system, arthritis etc., when immune system starts attacking it's own cell environment or dermis areas. Five types of psoriasis has observed in human. Cell division cycle gets smaller, and abnormal dead cell gets scaly and deposits in the skin. DNA methylation, histone modification and microRNA modification are the epigenetics behind psoriasis. Skin aging takes place due to the accumulation of macromolecules, such as DNA, proteins, lipids etc. It gets deoxidized because of atomic oxygen or reactive oxygen species (ROS).

Because of ROS mitochondria gets damaged. Mitochondria are the power house of a cell that produces ATP. ATP is required in any biosynthetic pathways as a source of energy. The production of ROS shuts down mitochondrial electron transport, it creates oxidative stress, followed by production of more ROS. It shortens the telomere of chromosomes and creates cell cycle aging and cell cycle arrest also takes place. Oxygen is a big electron acceptor. Due to ROS and lack of oxygen cells produce superoxide radicals (O_2-) that is not available for cells respiration.

Generally, prolonged UV exposure causes damage to DNA and forms di-sulfide bridges. Various forms of dermatitis like eczema or chemicals induce inflammation and pigmentation. Inflammation causes swelling followed by death of dermis and excess melanin production takes place. During pregnancy, excess pigmentation also takes place, it's called pregnancy mask. It happens due to overproduction of hormones. Tyrosine is the precursor of melanin.

Tyrosinase enzyme converts tyrosine into melanin. Oxidization of tyrosine followed by it's polymerization produces melanin pigment. It is possible that the amino acid side chains of tyrosine accept protons and polymerization takes place. *In vitro* polymerization happens at basic pH. After UV exposure melanocyte cells activate cytokines and produce NO (nitric oxide) and activate whole signal transduction pathway, that eventually produces melanin in the cytoplasm [70].

Method

Pyrosequencing is required to find DNA methylation. This technique based on the release of pyrophosphate in every nucleotide incorporation. One of the sequencing PCR primer should be biotynilated. It's incorporation emits light and eventually produces pyrogram. Pyrosequencing and MALDI-TOF are used to find the precise position of methylation. General formula for MALDI-TOF matrix is acetonitrile, water, trifluoroacetic acid (50:48:2). Bacterial and fungal cell smear or cell extract gets used for this experiment. This technique measures peptides and other compounds in presence of salts [71-73].

Multi fluorophore associated in-situ hybridization shows the pattern of gene activation in cells. Some genes get hypermethylated during Alzheimer's disease. knock out mutation helps to find the specific gene. Brain cells or neuron can be sectioned and stained differentially, and observed by confocal microscopy. Laser pulse in MALDI-TOF causes excitation of matrix molecules followed by energy transfer in gas phase matrix ion production. Bacterial sample volume should be optimal for MALDI-TOF.

PCR is an essential technique that helps to amplify any DNA sequence or genes. *In vitro* assay with high calcium concentration shows that high calcium makes brain cell dysfunctional. Or *In vitro* experiment shows that amyloid plaque can be dissociated with high acidic condition. polymerization assay helps to detect microtubule polymerization procedure in vitro. Lyophilized tubulin comes with the market available kits. One of the component of this kit is fluorophore, that helps with the high through put scanning and detection.

Generally, people use MRI scan to detect Alzheimer's. It is a radiation less examination technique, and takes about 30 minutes. MRI machine can produce images in any plane. Now with the advanced software people can dissect images in different planes and take series of pictures too. Isotope based dye can also be used with MRI. Allergic patients can react with this MRI dye.

Discussion

The versatilities of epigenetics show that it has effect in plants, animals, insects too. Epigenetic change enters through the food chain. Harmful chemicals in the soil or in the air also affects plants and animals. CGI promoter hypermethylation is not directly related to gene silencing, nearby sequence needs to be orchestrated with CGI methylation. All these reasons change chromosome's three-dimensional structure. In vertebrates methylated CGI promoter controls the gene expression. 70% genes are associated with this. Remote CGI also controls gene expression. It also supports the jumping gene theory and gene inactivation by remote control sequences. DNA is not randomly located in the nucleus, it resides in the nucleosome. The enzyme causes DNA methylation that also resides in the nucleosome [74-78].

Some researchers also thought that short peptides that block ribosomes can also be the reason for Alzheimer's. Immature peptides especially made with hydrophobic amino acids can form plucks. Again, everything is related to gene transcription. According to epigenetic data's and current research, tells that Alzheimer's is a disease that happens in older age, the brain gets clogged with dysfunctional peptides which body cannot dispose. Autophagy, apoptosis and cell death takes place eventually. Insulin down regulation causes glucose unavailable for the body. Less energy for cellular work.

It causes mitochondrial dysfunction and hampers ATP production. It triggers apoptosis, chromosomal breakage, and eventual cell death. Up regulation of arachidonic acid causes Apoptosis, p^{38} MAPK, intracellular calcium signaling also hampers. Genes in chromosomes 21, 14, 1 are associated with Alzheimer's. When mutation takes place, generally one amino acid gets replaced by others. If hydrophilic amino acid gets changed by hydrophobic amino acid, proteins φ, ψ angle gets changed followed by docking pattern of protein changes or chromosomal three-dimensional structure. It has reported that down syndrome people develop Alzheimer's because they carry an extra copy of chromosome 21. This chromosome 21 carries genes for the amyloid beta [79].

Stress, depression, and anxiety are all related to each other. Lack of serotonin causes depression. Several environmental factors can cause depression. It is a multi-branch biosynthetic pathway. Stress induced sickness is a headache, ulcer, infection with various microbes etc. Stress suppress the immune system and it makes the body vulnerable to various kind of health issues. Stress causes the stomach to secrete excess hydrochloric acid. Excess acid damages stomach cell lining and chronic acidity take place. Stress induced injury can come from the battle ground or from everyday life chores. Any skin wound can bring infection from microbes. It has already discussed that oxidative stress disrupts whole cell's biosynthetic pathways. The headache comes from working or exercising long hours under the sun or in a nosy work place. The stressful job gives muscle spasm, neck shoulder pain and eventually migraine. When people are stressed, they often exercise less and sometime stay inside the room, which is not full of oxygen. It creates oxidative stress. Various childhood viral infection can stay in rudimentary condition for a long period time in the body. In the later life, it causes allergy or skin diseases. Stress suppresses the immunity but humoral immunity stays active [80].

Phenylketonuria is a unique genetic disorder where babies are born without the capability to break down amino acid phenyl alanine. This reaction eventually produces pigment melanin in the body. Baby's secret excess phenyl alanine in urine which is pigmented and smelly. Here enzyme phenylalanine hydroxylase which converts phenylalanine to tyrosine either gets mutated or absent. In presence of cofactor BH_4 and molecular O_2 L-tyrosine. These babies need a special diet. If they take normal diet, they develop mental retardation, abnormal teeth etc. Mutation in both alleles of gene phenylalanine hydroxylase in chromosome 12 is related to phenylketonuria [81].

Food born or environment born allergies are also part of epigenetics. Various food can cause Asthma and atopic dermatitis. Over active immune system can react with any food in the gut lining. People with a liver problem and enzyme secretion can produce allergy as well. Their body cannot break the food molecules and stay in the body for a long time, eventually, kidney gets affected.

Seasonal change can increase pollen production which causes allergy. An elevated level of CO2 and ground level ozone also trigger an allergy. Hyper immune system and normal immune system both gets affected by seasonal change. Over production of IgG makes the body warm. Nasal passage gets swollen followed by less oxygen in the brain and people get headache. Due to inversion air dust and virus particle linked with causes allergy. Over production of IgE, IgA, IgG can produce anaphylaxis type symptom. Generally, the body breaks down big food particles with the help of the liver enzymes. If the liver is weak it takes a long time to break food molecules. Bigger food molecule cannot get cleaned by the kidney and stays in the body for a long time.

That also causes allergy. To boost liver activity several natural food helps. Papain enzyme from papaya helps the liver function. Telomere length and histone's presence is very important in cells. Tight histone packaging protects telomere from breakage and methylation. Methyl group from food can cause methylation of histone and oxidation. Too long telomere can cause recombination. It is also the reason for cancer.

Folate or folic acid protects telomere from fragmenting. Broken telomere creates sticky ends. Chromosomes stick to each other, and during cell division uneven chromosomal division takes place. Folate provides the precursor molecules that catalyzes S adenosine-methionine (SAM). During pregnancy, mothers are advised to eat food that is full of folate. It prevents fragile X chromosome related problems. Polyphenols are available in fruits and vegetables, especially pigmented fruits. Grapes are a good source of polyphenols. Polyphenol stops oxidation. It also stops telomerase enzyme. Telomerase enzyme adds nucleotides at the end of telomere and makes it extra long. Polyphenol stops telomerase. Drug makers already targeted histones. Histone deacetylase prevents histone from condensation and keeps gene open for transcription [82].

Allergy and asthma attack is very common during the spring season. In US average 50 million people get affected by this. DNA methylation and histone modification is also part of it. When histone is loosely arranged mRNA or DNA polymerase can access the sequence but when histone is tightly arranged it makes the gene unavailable for transcription. Due to various cellular stress signal DNA methyltransferase adds a methyl group in cytosine position five in CpG island. These CpG are palindromes.

That's why during cell division they get recognized and transferred to daughter cells. CpG islands are part of promoter and enhancer sites. This methylated cytosine can produce various derivatives too. It is possible that these methylations can stop transcription factors by recruiting CpG binding proteins. Histone acetylation and phosphorylation is the active state of histone. Methylation makes the genes unavailable to translate.

Granulocytes, macrophages and NK cells are body's natural immune system. These cells produce atomic oxygen to kill microbes or macrophage engulfs the microbes and enzyme degradation takes place. Macrophages always sweep through the blood system and kill unwanted microbes. Macrophages releases cytokines that help with communication during infection. IL 1-IL6 and tumor necrosis factor (TNFα) are the proinflammatory factors. When the body is stressed, it produces different hormones from pituitary or hypothalamus. That interferes with other growth hormones and infection related cell signaling pathways. The essential molecular binding site gets competitive or unavailable, that's how during stress immune system gets suppressed. Sometimes people under stress consume lot of alcohol. Alcohol is not body's natural product, it also hampers molecular interactions.

Cancer develops due to miRNA methylation in CpG site. Several research pointed out that early miRNA detection will be the key parameter to stop cancer development. miRNAs are 22 nucleotides long and control gene's activity post-transcriptionally. miRNA genes are located within the intergenic location and codes reside in the exonic and intronic region, possible to read in sense and antisense directions. They are the noncoding RNA. When RNA binds respective genes, it makes the gene inactive. All kinds of cancer start with miRNA methylation. Although half-life of RNA is short, some companies already advanced to detect cancer from a drop of blood.

ROS reacts with nucleic acid, protein, lipid, and sugar. Oxidation of lipid reduced sugar and protein produce carbonyl and carbonyl adducts e.g. 4 hydroxynonanal (HNE). During protein degradation, either peptide bond or side chains gets targeted. The addition of carbonyl group dismantles proteins. HNE reacts with nucleophilic side chains of nucleic acid. HNE makes the protein irreversibly alkaline. Most of the time enzymes are made of proteins that have several subunits. Deletion of one subunit can make the enzyme inactive. In a biosynthetic pathway when one essential enzyme degrades the whole forward reaction stops; followed by accumulation of extra electrons in the surrounding areas that produce even more atomic oxygen. Eventually, cell dies.

ATP level varies in normal cells and a diseased cell. ATP is the energy carrier in different cells. Most of the time mitochondria gets affected in diseased cells. It depletes ATP production. Without ATP or source of the electron, the biosynthetic pathway cannot move forward. In absence of ATP and electron transport respiratory chain reaction goes down. Eventually, apoptosis takes place. The level of ATP controls the folding and expression of growth factor receptors.

These are also proteins. Glucose is the source of energy in any cell. Hexosamine biosynthetic pathway provides glucose in the cell. All the sub organelles activities are correlated to each other, especially ATP molecule provides energy in every reaction. Down regulation of ATP synthesis causes pro-apoptosis in the cell. ATP deprivation takes place in any type of apoptotic cells. Mitochondrial dysfunction and ATP deprivation is the hall mark of cancer cells as well as in other diseases. Alzheimer's cells also deprive of ATP. It proves that energy requirement is universal in the whole living world.

Mitochondrial biogenesis and proliferation of peroxisome are correlated, and it is controlled by PGC- 1α gene expression. The receptor gamma coactivator 1α (PGC-1α) proliferates peroxisome. FOXO gene family controls the muscle degradation through ubiquitin proteasome pathway and by lysosome autophagy. Due to oxidative stress muscles are prone to degrade. The epigenetic modification takes place by histone acetylation. Exercise upregulates mitochondrial biogenesis. Exercise takes off ROS and helps with mitochondrial proper function. Natural suppliments like vitamins, minerals and antioxidants has the capability to absorb free radicals like ROS, and it improves mitochondrial activity [83].

Smoking is hazardous and it has epigenetic influence in human body. It can cause lung and upper respiratory tract cancer. If the mothers smoke during pregnancy, their kids show intelligence impairment compare to those kids whose mother never smoked. Fetal brain exposure to nicotine and acetylcholine nicotine receptors at the early stages of brain development causes the problem in later age. Smoking causes various diseases that include chronic pulmonary disease, chronic bronchitis, lung cancer, cancer of larynx etc.

Smoking is related to DNA methylation and cardiovascular disease. This methylation pattern changes during cell division and tissue differentiation. In every disease, gene silencing takes place through miRNA. S-nitrosylation represses phosphorylation of key elements in cytokine signalling pathway. SWI and SNF is the product of SWI and SNF genes. It is a multi subunit protein complex and takes part in DNA remodeling and responds to alcohol. SWI/SNF has two subunits AWSN-9 and SWSN-7 is required for neuronal cells and muscle development and responds to alcohol tolerance. The activity of these subunits proves that DNA remodeling is required for alcohol tolerance [84-87].

Several epigenetic drugs are in clinical trial now. It targets DNA methylation and histone acetylation. DNA repair enzyme MGMT, alkylating agent carmustine and temozolomide can be used for chromatin remodeling. A type of drug targets DNA methyl transferases

and another targets histone acetylases in case of cancer. 5 Azacytidine stops DNA methylation that has observed closely in experimental objects. The trade mark of 5 Azacytidine is Vidaza, a product of Celgene Corporation. Dacogen also stops methylation. Histone deacetylase inhibitor drugs such as Vorinostat and Romidepsin showed promising results. Some cancer drugs are under clinical trial (bromodomain) that target histones.

Folic acid, valproic acid, sulfasalazine can change DNA methylation. Recent research trends also show that several long-term infections can cause cancers. DNA methylation is very common in cancer diseases. 125 DNA methylation sites has observed in colon cancer. Cancer related genes SNF5 and EZH2 has targeted to build epigenetic drugs. EZH2 is a small target for epigenetic medicine. And its inhibitor binding site is also competive with S adenosyl methionine. The approach of antibody targeted poteins involved in epigenetics has its infancy now. Immunoprecipitation of these proteins is possible *in vitro* but how far will it be active *invivo*, its yet to be confirmed.

Several small molecules are in phase I clinical trial, such as EZH2, DOT1Land BET inhibitors. BET inhibitors are bromodomain inhibitors. To inhibit DOT1L shRNA has used. Enantiomers are important molecular structures that should be analyzed and applied to produce new drugs. Protein or enzymes docking sites get changed due to rotational changes in amino acids and eventual structural changes in chromatin. In that case enantiomeric drugs can be useful. Although production of enantiomer in painstaking and costly. Inactive enantiomers can be toxic to health. Most of the biological molecules are chiral, such as proteins, enzymes, fat, sugar etc. FDA approved drugs are also come in chiral form.

Some experimental drugs are already in the clinical trial that contains crystals of isomers and enantiomers. Pure active crystals of enantiomers will be worth to apply in diseases that has developed due to histone methylation in chromosomes [88-92].

Effect of Environment

It is already well experimented that environmental pollution can cause an epigenetic change in animal, plants, and insects. The honey bees produce worker and queen bee by differentiating their diet. Queen bee gets royal jelly food, probably that helps the bee to get bigger in size. In tropical areas, especially near the line of cancer, people get scotch sun light. Human body produces excess melanin to protect cells from UV radiation. It affects their skin and melanin formation. People get darker. This is also considered epigenetic effect. Human body produces excess melanin to protect cells from UV radiation.

It has reported that certain polyphenols stop cancer. Soybean mimics female fertility hormone such as estrogen. This dietary effect is epigenetic. Through metabolic pathway, people started supplying essential molecules to stop methylation. Arsenic poisoning from the water gives rise to stomach ulcer and a type of skin cancer. It produces black or brown puffy irregular circle in the skin and causes irritation. A lot of infections come from water born bacteria's. And it infects bigger mass of the population. Infected water makes vegetable poisonous too. Several *E. coli* outbreaks occurred in the past due to poorly washed vegetables. Virus particle or bacterial spores reside in dust particle and it causes upper respiratory tract infections. Sometimes these infections are long lasting and cause other side effects. Viral or bacterial proteins compete with essential cellular proteins.

Peroxisome proliferator trichloroethylene, dichloroacetic acid, trichloroacetic acid, air pollutant carbon, benzene, endocrine disrupting toxin bisphenol, dioxin are the environmental agents that create epigenetic changes. Histone H_3 and H_4 has a long protruding tail that can modify nucleosome structure by acetylation, ubiquitination, phosphorylation, methylation, sumoylation, and citrullination. These changes chromatin structure and gene expression. Cadmium has a low mutagenic effect but it inhibits methylation by inhibiting DNA methyltransferases; whereas arsenic is highly mutagenic. Arsenic changes p^{53} and p^{16} promoters that were observed in the blood sample. Chromium causes methylation of p^{16}. Nickel binds to the histidine H_4 and creates a secondary structure [93-97].

Effect in Plants

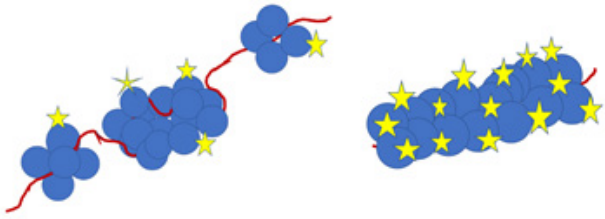
The very prominent epigenetic effect is present in plants. It is mitotically and meiotically inheritable but does not change DNA sequence. Flowering, photoperiodism, systematic tissue movement, seed vernalization, germination, and heterosis is controlled by

epigenetics. This mechanism is beneficial in the agricultural field. Longer fruiting and flowering time can be shortened by epigenetics. Short exposure with infrared light helps with germination. Temperature is another factor that controls plant growth in a bigger fashion.

The growing evidence shows that epigenetics and environment have the big impact together. Photovoltaic movement is present in plants e.g. sunflower. Some flowers and leaves move according to the movement of the sun. NO (nitric oxide), controls stress induced methylation in plants. It has observed in *Arabidopsis thaliana*. NO induce protein methylation through S-nitrosylation. PRMT5 (protein arginine methyl transferase 5) controls a lot of physiological process in plants. This enzyme exists in human as well as in mouse too. S-nitrosylation and PRMT 5 causes cross talk after translation. Environmental stress causes the production of NO. Nuclear DNA methylation is dominant in plants. Methylation is species, organelles, tissue and age specific in plants. Mitochondrial methylation is different in plants and it exist mostly in the nucleus. Herbivore attack and pathogen triggers the plant to secret hormones and eventually it gain resistance [98].

Conclusion

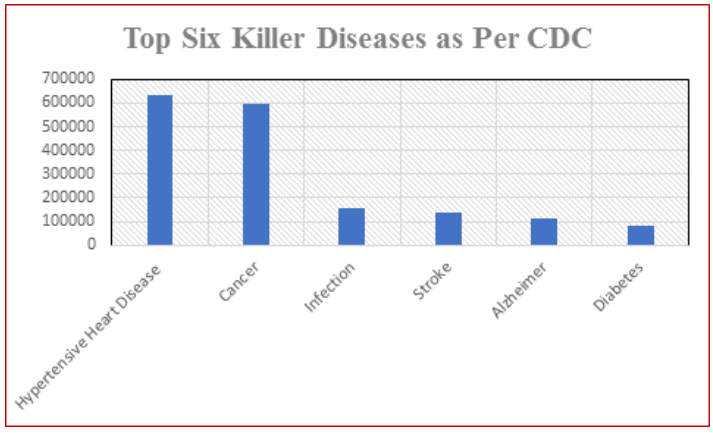
Epigenetics showed that the global warming, pollution, random food habit, lack of exercise can cause an enormous change in the human body. For decades, we knew that DNA and genes are the reasons for any health-related problems or diseases. Recent evidence showed that DNA methylation, histone modification, and some environmental factors control gene's activity and followed by overall changes in the body. Scientists have targeted histones deacetylation to form new drugs.



1 2

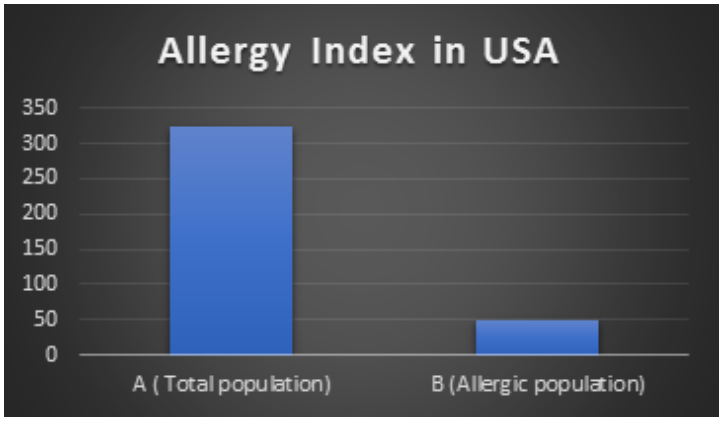
1. This cartoon picture represents histone modulation or modification and DNA oxidation, lose part of the DNA is accessible for translation.
2. A full methylated DNA where histone is modulated.

Graphical Representation of Top Six Killer Diseases



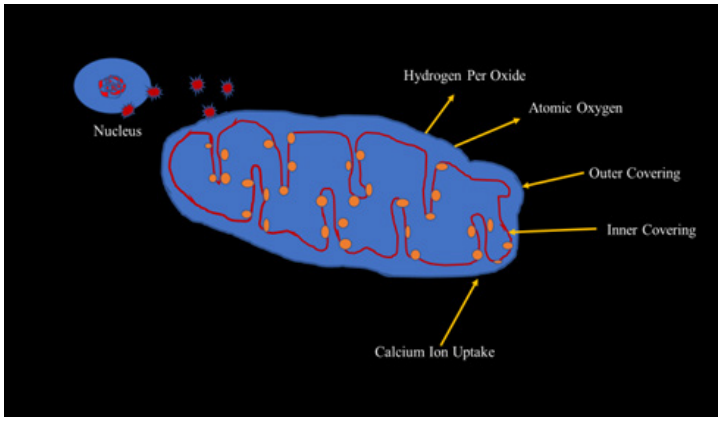
All these diseases can occur due to epigenetic changes in genes. Some of these diseases correlated to each other.

Epigenetic Effect in Allergy



A graphical representation of allergic population in US as per CDC

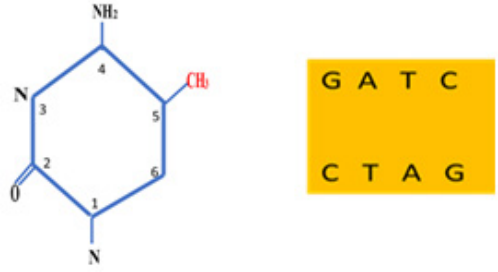
Apoptosis Induction in Mitochondria, Proapoptotic Proteins Invades Nucleus



This cartoon represents a mitochondrion that contains an outer layer and inner layer. Mitochondria produce hydrogen per oxide and under stressed condition produces atomic oxygen. A higher level of calcium ions in the mitochondria perturbs all mitochondrial activities. Pro apoptotic protein produced by lysosomal vesicles invades nucleus and starts DNA fragmentation.

This Cartoon Represents DNA methylation in Cytosine's Position Five, and an example of Palindrome Sequence

1 2



1.Cytosine methylation in position five 2. Palindrome sequences are readable from both sides, 5' to 3' and 3' to 5'. Palindrome Sequences are present in CpG site. During cell division, two DNA strand separates and each daughter cell gets one methylated strand.

Dedication- This paper is dedicated to me beloved father and the inspiration of my life Mr. H. N. Barman, An Executive magistrate of India Government.

References

1. Simmns D. "Epigenetic influences and Diseases". *Nature Education* 1.1 (2008): 6.
2. Khavari DA., *et al.* "DNA methylation and epigenetic control of cellular differentiation". *Cell Cycle* 9.19 (2010): 3880-3883.
3. Deaton AM and Bird A. "CpG islands and regulation of transcription". *Genes & Development* 25.10 (2011): 1010-1022.
4. Sun G., *et al*. "Epigenetic histone methylation modulate fibrotic gene expression". *Journal of the American Society of Nephrology* 21.12 (2010): 2069-2080.
5. Guo H., *et al*. "DNA methylation and chromatin accessibility profiling of mouse and human fetal germ cells". Cell Research 27.2 (2017): 165-183.
6. Ling C and Groop L. "Epigenetics: A molecular link between Environmental factors and Type 2 Diabetes". *Diabetes* 58.12 (2009): 2718-2725.
7. Gilbert ER and Liu D. "Epigenetics: the missing link to understanding β cell dysfunction in the pathogenesis of type two diabetes". *Epigenetics* 7.8 (2012): 841-852.
8. Ling C and Groop L. "Epigenetics: A molecular link between Environmental factors and Type 2 Diabetes". *Diabetes* 58.12 (2009): 2718-2725.
9. Rea IM. "Towards aging well, Use it or lose it, Exercise, epigenetics and cognition". *Biogerontology* 18.4 (2017): 679-691.
10. Meier JL. "Metabolic mechanism of epigenetic regulation". *ACS Chemical Biology* 8.12 (2013): 2607-2621.
11. Chen S., *et al*. "Transcriptional coactivator p300 controls glucose induced gene expression in endothelial cells". A*merican Journal of Physiology - Endocrinology and Metabolism* 298.1 (2010): E127-E137.
12. Johnson C., *et al*. "Epigenetics and Cancer Metabolism". *Cancer Letters* 356.2 (2015): 309-314.
13. Suzuki H., *et al*. "DNA methylation and microRNA dysregulation in cancer". *Molecular Oncology* 6.6 (2012): 567-578.
14. Israelsen WJ and Heiden M G V. "ATP consumption promotes Cancer Metabolism". *Cell* 143.5 (2010): 669-671.
15. Zhou Y., *et al*. "Intracellular ATP levels are a pivotal determinant of chemoresistance in colon cancer cells". *Cancer Research* 72.1 (2012): 304-314.
16. Barnicle A., *et al*. "Differential DNA methylation patterns of homeobox gene in proximal and distal colon epithelial cells". *Physiological Genomics* 48.4 (2016): 257-273.
17. Falkenberg KJ and Johnstone RW. "Histone deacetylases and their inhibitors in cancer, nurological diseases and immune disorders". *Nature Reviews Drug Discovery* 13.9 (2014): 673-691.
18. Sharma S., *et al*. "Epigenetics in Cancer". *Carcinogenesis* 31.1 (2010): 27-36.
19. Toiyama Y., *et al*. "DNA methylation and microRNA biomarkers for noninvasive detection of gastric and colorectal cancer". *Biochemical and Biophysical Research Communications* 455.1 (2014): 43-57.
20. Wainwright EN and Scaffidi P. "Epigenetics and cancer stem cells: unleashing, hijacking and restricting cellular plasticity". *Cell Metabolism* 3.5 (2017): 372-386.
21. Sarkar D., *et al*. "Epigenetic regulation in human melanoma: past and future". *Epigenetics* 10.2 (2015): 103-121.
22. Sharma S., *et al*. "Epigenetics in Cancer". *Carcinogenesis* 31.1 (2010): 27-36.
23. Park SY., *et al*. "Distinct pattern of promoter CpG island methylation of breast cancer subtypes are associated with stem cell phenotypes". Modern Pathology 25.2 (2012): 185-196.
24. Gautery HE., *et al*. "DNA methylation abnormalities at gene promoters are extensive and variable in the elderly and phenocopy cancer cells". The FASEB Journal 28.7 (2014): 3261-3272.
25. Chen J., *et al*. "Variation in carbohydrates between cancer and normal cells memebrane revealed by super resolution fluorescence imaging". *Advanced Science* 3.12 (2016): 1600270.
26. Khalil CA. "The emerging roles of epigenetics in cardiovascular disease". *Therapeutic Advances in Chronic Disease* 5.4 (2014): 178–187.

27. Webster A LH., *et al*. "Epigenetics and cardiovascular disease". *Canadian Journal of Cardiology* 29.1 (2013): 46-57.
28. Turgeon PJ., *et al*. "Epigenetics and cardiovascular disease – a new beat in coronary artery disease". *Medical Epigenetics* 2.1 (2014): 37-52.
29. Webster A LH., *et al*. "Epigenetics and cardiovascular disease". *Canadian Journal of Cardiology* 29.1 (2013): 46-57.
30. Wise IA and Charchar FJ. "Epigenetic Modification in Essential Hypertension". *International Journal of Molecular Sciences* 17.4 (2016): 451.
31. J Wang., *et al*. "Hypertensive epigenetics: from DNA methylation to microRNAs". *Journal of Hypertension* 29.10 (2015): 575-582.
32. Harrison DG. "The immune system in hypertension". *Transactions of the American Clinical and Climatological Association* 125 (2014): 130–140.
33. Mut J V S and Graff J. "Epigenetic alteration is Alzheimer's disease". *Frontiers in Behavioral Neuroscience* 9 (2015): 347.
34. Qazi TJ., *et al*. "Epigenetics in Alzheimer's disease: perspective of DNA methylation". *Molecular Neurobiology* (2017).
35. Ding Q., *et al*. "Ribosome dysfunction is the early event in Alzheimer's disease". *Journal of Neuroscience* 5 .40 (2005): 9171-9175.
36. Murphy MP and Levine H III. "Alzheimer's disease and the β amyloid peptide". *Journal of Alzheimer's Disease* 19.1 (2010): 311.
37. Orr M E and Oddo S. "Autophagic/Lysosomal dysfunction in Alzheimer's disease". *Alzheimer's Research & Therapy* 5.5 (2013): 53.
38. Nixon RA. "Autophagy, amyloidogenesis and Alzheimer disease". *Journal of Cell Science* 120 (2007): 4081-4091.
39. Andrea S., *et al*. "Decreased methylation of the mitochondrial D-loop region in late onset Alzheimer's disease". *Journal of Alzheimer's disease* 59.2 (2017): 559-564.
40. Chandra A., *et al*. "Genetic and epigenetic basis of psoriasis pathogenesis". *Molecular Immunology* 64.2 (2015): 313-323.
41. Reiner SL. "Epigenetic control in the immune response. *Human Molecular Genetics* 14.1 (2005): R41-R46.
42. Obata Y., et al. "Epigenetic modifications of the immune system in health and disease". *Immunology and Cell Biology* 93 (2015): 226-232.
43. Cuevas A., *et al*. "Modulation of immune function by polyphenols: Possible contribution to epigenetic factors". *Nutrients* 5.7 (2013): 2314-2332.
44. Uddin M., *et al.* "Epigenetic and immune function profile associated with post-traumatic stress disorder". *Proceedings of the National Academy of Sciences* 107.20 (2010): 9470–9475.
45. Segerstrom SC and Miller GE. "Psychological stress and human immune system: A Meta analytic study of 30 years of enquiry". *Psychological Bulletin* 130.4 (2004): 601-630.
46. Begin P and Nadeau KC. "Epigenetic regulation of Asthma and allergic disease". *Allergy, Asthma & Clinical Immunology* 10.1 (2014): 27.
47. Fernandaz MJL., *et al*. "Epigenetic regulation of immune system in health and disease". *Tissue Antigens* 76.6 (2010): 431-439.
48. MacDonald IA and Hathaway NA. "Epigenetics roots of immunological diseases and new methods for examining chromatin regulatory pathways". *Immunology and Cell Biology* 93.3 (2015): 261-270.
49. Richardson B. "Primer: epigenetics of autoimmunity". *Nature Clinical Practice Rheumatology* 3.9 (2007): 521-527.
50. Hedrich CM. "Epigenetics in SLE". Current Rheumatology Reports 19.9 (2017): 58.
51. Wu H., *et al*. "Critical link between Epigenetics and Transcription factors in the induction of autoimmunity: a comprehensive review". *Clinical Reviews in Allergy & Immunology* 50.3 (2016): 333-344.
52. Araki Y and Mimura T. "The histone modification code in the pathogenesis of autoimmune diseases". *Mediators of Inflammation* (2017).
53. Perera MN., *et al*. "Ceramide channels: influence of molecular structure on channel formation in memebranes". *Biochimica et Biophysica Acta (BBA) - Biomembranes* 1818. 5, (2012): 1291-1301.
54. Chakrabarti S., *et al*. "Experimental evidences of water mediated electron transfer through bis amino acid donor bridge acceptor oligomers". *Journal of the American Chemical Society* 131.6 (2009): 2044-2045.
55. Doelle H W. "Cell thermodynamic and energy metabolism". BIOTECHNOLOGY – Vol. I – book.
56. Demirel Y. "Thermodynamics and bioenergetics". *Biophysical Chemistry* 97.2-3, (2002): 87-111.

57. Lucia U. "Bioengineering and thermodynamics of biological cells". *Theoretical Biology and Medical Modelling* 12: 29 (2015).
58. Crews D. "Epigenetics and its implication for behavioral neuroendocrinology". *Frontiers in Neuroendocrinology* 29.3 (2008): 344-357.
59. Siniscalco D., *et al*. "Epigenetic findings in Autism: New perspective for therapy". *International Journal of Environmental Research and Public* 10.9 (2013): 4261-4273.
60. Loke YJ., *et al*. "The role of epigenetic change in Autism spectrum disorder". *Frontiers in Neuroendocrinology* 6 (2015): 107.
61. Pal S and Tyler JK. "Epigenetics and aging". *Science Advances* 2.7 (2016): e1600584.
62. Antell D E and Takzanowski EM. "How environment and life style choices influence the aging process". *Annals of Plastic Surgery* 43.6 (1999): 585-588.
63. D'Aquila P., *et al*. "Epigenetics and aging". *Maturitas* 74.2 (2013):130-136.
64. Moghadam BT., *et al*. "Combinational indentification of DNA methylation patterns over age in the human brain". *BMC Bioinformatics* 17.1 (2016): 393.
65. Otterdijk SD van., *et al*. "Do age related changes in DNA methylation play a role in the development of age related diaeases?" *Biochemical Society Transactions* 41.3 (2013): 803-807.
66. Bekaert S., *et al*. "Telomere attrition as aging biomarker". *Anticancer Research* 25.4 (2005): 3011-3021.
67. Gronninger E., *et al*. "Aging and Chronic sun exposure cause distinct epigenetic changes in Human skin". *PLOS Genetics* 6.5 (2010).
68. Colyer HAA., *et al*. "Detection and analysis of DNA methylation by pyrosequencing". *Cancer Epigenetics* (2012): 281-292.
69. Celebi OO., *et al*. "Detection of O6 methyl guanine DNA methyl transferase gene promoter region methylation pattern using pyrosequencing and the effect of methylation pattern on survival recurrence and chemotherapy sensitivity in pateints with lyringial cancer". *Pathology Research and Practice* 212. 5 (2016): 456-462.
70. Angeletti S. "Matrix assisted laser desorption time of flight mass spectrometry (MALDI-TOF-MS) in clinical microbiology". *Journal of Microbiological Methods* 138 (2017): 20-29.
71. Ficociello B., *et al*. "Epigenetics and environmental exposure to xenobiotics". *G Ital Med Lav Ergon* 32.1 (2010): 13-22.
72. Crews D. "Epigenetics, brain, behavior and the environment". *Hormones* 9.1 (2010): 41-50.
73. Aguilara O., *et al.* "Epigenetics and Environment: a complex relationship". *Journal of Applied Physiology* 109.1 (2010): 243-251.
74. Koestler DC., *et al*. "Blood based profiles of DNA methylation predict the underlying distribution of cell types". *Epigenetics* 8.8 (2013): 816-826.
75. Zhang G and Pradhan S. "Mammalian epigenetic mechanisms". *IUBMB Life* 66.4 (2014): 240–256.
76. Nicolson GL. "Mitochondrial dysfunction and chronic disease: treatment with natural suppliments". *Integrative Medicine (Encinitas)* 13.4 (2014): 35-43.
77. AM Stankiewicz., *et al.* "Epigenetics of stress adaptation in the brain". *Brain Research Bulletin* 98.76.92 (2013): 76-93.
78. Williams RA., *et al*. "Phenylketonuria: An inbron error of phenylalanine metabolism". *Clinical Biochemist Reviews* 29.1 (2008): 31-41.
79. Marioni RE., *et al*. "The epigenetic clock and telomere length are independently associated with chronologial age and mortality". *International Journal of Epidemiology* 45.2 (2016): 424-432.
80. Saughnessy DT., *et al*. "Mitochondria Energentics, Epigenetics and cellular response to stress". *Environmental Health Perspectives* 122.12 (2014): 1271-1278.
81. Boccuto L and Abenavoli L. "Genetic and Epigenetic Profile of Patient with Alcoholic Liver Disease". *Annals of Hepatology* 16.4 (2017): 490-500.
82. Breitling LP. "Current genetics and epigenetics of smoking/tobacco related cardiovascular disease". *Arteriosclerosis, Thrombosis and Vascular Biology* 33.7 (2013): 1468-1472.
83. Knopik VS and Maccani MA. "The epigenetics of maternal cigarette smoking during pregnancy and effects on child development". *Development and Psychopathology* 24.4 (2012): 1377-1390.
84. Mathies LD., *et al*. "SWI/SNF chromatin remodeling regulates alcohol response behaviors in Caenorhabditis elegans and is associated with alcohol dependence in human". *Proceedings of the National Academy of Sciences* 112.10 (2015): 3032-3037.

85. Szyf M. "Epigenetics, DNA methylation, and chromatin modifying drugs". *Annual review of Pharmacology and Toxicology* 49 (2009): 243-263.
86. Peedicayil J. "Epigenetic therapy – a new development of pharmacology". *Indian Journal of Medical Research* 123 (2006): 17-24.
87. Campbell RL and Tummino PJ. "Cancer epigenetic drug discovery and development: the challenge of hitting the mark". *Journal of Clinical Investigation* 124.1 (2014): 64-69.
88. Rius M and Lyko F. "Epigenetic cancer therapy: rationales, targets and drugs". *Oncogene* 31.39 (2012): 4257-4265.
89. Sekhon BS. "Enantioseparation of chiral drugs- An Overview". *International Journal of Pharm Tech Research* 12.2 (2010): 1584-1594.
90. Feil R and Fraga MF. "Epigenetics and the environment: emerging pattern and implications". *Nature Reviews Genetics* 13 (2012): 97-109.
91. Baccarelli A and Bollati V. "Epigenetics and environmental chemicals". *Current Opinion in Pediatrics* 21.2 (2009): 243-251.
92. Feil R and Fraga MF. "Epigenetics and the environment: emerging patterns and implications". *Nature Reviews Genetics* 13 (2012): 97-109.
93. Marsit CJ. "Influence of environmental exposure on human genetic regulation". *Journal of Experimental Biology* 218.1 (2015): 71-79.
94. Weinhold B. "Epigenetics: The science of change". *Environmental Health Perspectives* 114.3 (2006): 160-167.
95. Hu J., *et al*. "Nitric oxide regulates protein methylation during stress responses in plants". *Molecular Cell* 67.4 (2017): 702-710.
96. Vanyushin BF and Ashapkin VV. "DNA methylation in higher plants: past, present and future". *Biochimica et Biophysica Acta, Gene Regulatory Mechanism* 1809.8 (2011): 360-368.
97. Lauria M and Rossi V. "Epigenetic control of gene regulation in plants". *Biochemica et Biophysica Acta (BBA), Gene regulatory Mechanisms* 1809.8 (2011): 369-378.
98. Holeski LM., *et al.* "Transgenerational defence induction and epigenetic inheritence in plants". *Trends in Ecology & Evolution* 27.11 (2012): 618-626.

Submit your next manuscript to Scientia Ricerca Open Access and benefit from:

→ Prompt and fair double blinded peer review from experts
→ Fast and efficient online submission
→ Timely updates about your manscript status
→ Sharing Option: Social Networking Enabled
→ Open access: articles available free online
→ Global attainment for your research

Submit your manuscript at:
https://scientiaricerca.com/submit-manuscript.php