Dynamic Developments in Epigenetics

Urantia Foundation, Science Symposium 2022

June 16-18

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Epigenetics represents a recently discovered new level of control of the expression of genes in each of our cells that is altered by environmental factors such as experience, diet, psychic trauma, and human choice. We are all familiar with the expression "mind over matter," defined as, "used to describe **a situation in which someone is able to control a physical condition, problem, etc., by using the mind."** (Wikipedia) The ability to keep going even when tired, represents a common application of this concept.

The study of epigenetics involves a scientific examination focused on how environmental factors, experience, human choices, and other factors that influence or control a human genome without altering the DNA molecular structure. As a result of our rapidly expanding ability to study life at the molecular level, where we can actually observe the activity of atoms and molecules and trace their effects on living organisms, we have discovered metabolic pathways by which the epigenome controls which and when genes are expressed, and in particular how they direct embryologic and other developmental processes. A formal definition of epigenetics states:

I. Definition of epigenetics:

"Epigenetics is the study of how the expression of gene activity is controlled at the cellular level, without altering DNA molecular structure. "Epi" is Greek meaning above or beyond. In living cells, epigenetics, or the epigenome, exercises significant control over when genes are turned "on" or "off." (Wikipedia)

As students of *The Urantia Book,* we are familiar with the concept of mind control on a cosmic philosophical level and should not be surprised that it is also expressed scientifically at the molecular level.

A. Mind Over Body Is a Metabolic Reality.

"Mind is always creative. The mind endowment of an individual …is always competent to produce a suitable and serviceable body for the living creature identity."[1]

Sigismund von Dobschütz, CC BY-SA 3.0 <http://creativecommons.org/licenses/by-sa/3.0/>, via Wikimedia Commons

B. The cards we've been dealt are in our hands!

Each of us arrives on this world having received a set of hereditary factors consisting of a unique combination of genes from both of our parents, in the form of DNA. We will begin to recognize the strengths and weaknesses of the hand we've been dealt as we progressively become aware of our personal potentials. Opportunities to demonstrate our abilities, to express our needs and desires, and exercise the strengths of our unique personalities, will abound as our awareness of our surroundings expands. How we play our hand will have long-term consequences.

Epigenetics is an extension of this idea to the molecular level of living organisms. For example, a gene that controls the production of a specific protein when turned "off" will remain dormant until it receives a signal to turn "on" at which time it will initiate the process of assembling the specific amino acids, in the exact sequence of the required protein. In eukaryotes, the type of cells which compose multicellular organisms such as humans, the complete genome is located within the nucleus of *each cell throughout the entire body*. The epigenome can determine when and where the specific

genes will be expressed. It is a regulatory system that controls genetic expressions throughout the body, like a schedule or plan for gene expression.

An analogy of the functional relationship between the genome and epigenome can be crudely illustrated by a blueprint for a building, as contrasted with the building schedule. The blueprint is needed at each of the various sites where the building components are being manufactured. The genome serves as the blueprint. However, a building plan or schedule is required to manage the timing and sequence in which the various components of the building will be delivered and placed in final position, a function similar to that performed by the epigenome.

II. A brief review of human genetics

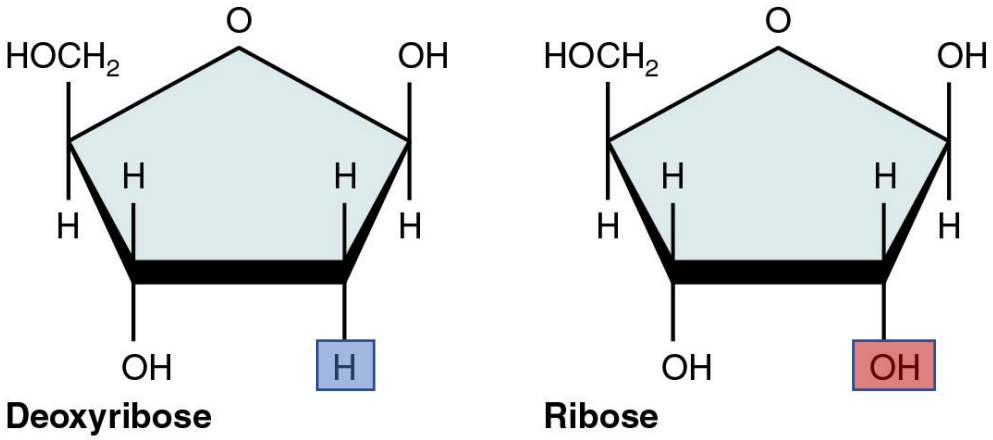
To understand how epigenetics controls and modifies genetics, a brief review of genetics is essential. DNA was first discovered by Franklin Miescher in the late 1800s, but it was nearly a century later before the significance of the molecule was recognized and its chemical structure determined.

In 1953, the combined work of James Watson, Francis Crick, Rosalind Franklin, and Maurice Wilkins led to the discovery that its basic structure was a double helix consisting of two long strands of deoxyribose sugar molecules, each with an associated phosphate group, forming a double stranded backbone with nucleotides arranged in parallel rows in the middle, held together by hydrogen bonds. There are four different nucleotides: cytosine, guanine, adenine and thymine. By convention, the first letter of each nucleotide's name is the letter used in the genetic language alphabet that encodes the names of the amino acids: C for cytosine, G for guanine, A for adenine, and T for thymine. The genetic information is encoded and stored by the nucleotides in genes. Whenever proteins are required to build or rebuild cells throughout the body, the genes for the required proteins are activated, the encoded information for making them is copied onto messenger RNA (mRNA) which is then sent to the ribosome where it is translated, and a protein is produced. The entire genome must be replicated for each new somatic cell required for replacement of old cells. This occurs approximately 10 million times per second in each of us throughout our lifetime.

The nucleotides always assume a paired configuration in which the adenine joins thymine and guanine joins cytosine, and vice versa. The former displays two hydrogen bonds and the latter three hydrogen bonds, resulting in slightly stronger attraction between the guanine-cytosine then the

adenine-thymine. It should be noted that otherwise, there are no differential chemical forces that can determine the sequential positioning of the nucleotides along DNA molecule.

A. Deoxyribose and Ribose Sugars Are Shown Below.



Deoxyribose and Ribose are single-ring pentose, or five carbon sugars. The numbering of the carbon atoms runs clockwise, following organic chemistry rules, starting from the carbon atom occupying the position farthest to the right in the ring. Note the absence of the oxygen atom from the hydroxyl group on the 2’ carbon in the deoxyribose sugar (highlighted in blue) in DNA as compared with the ribose sugar in RNA, (highlighted in red).

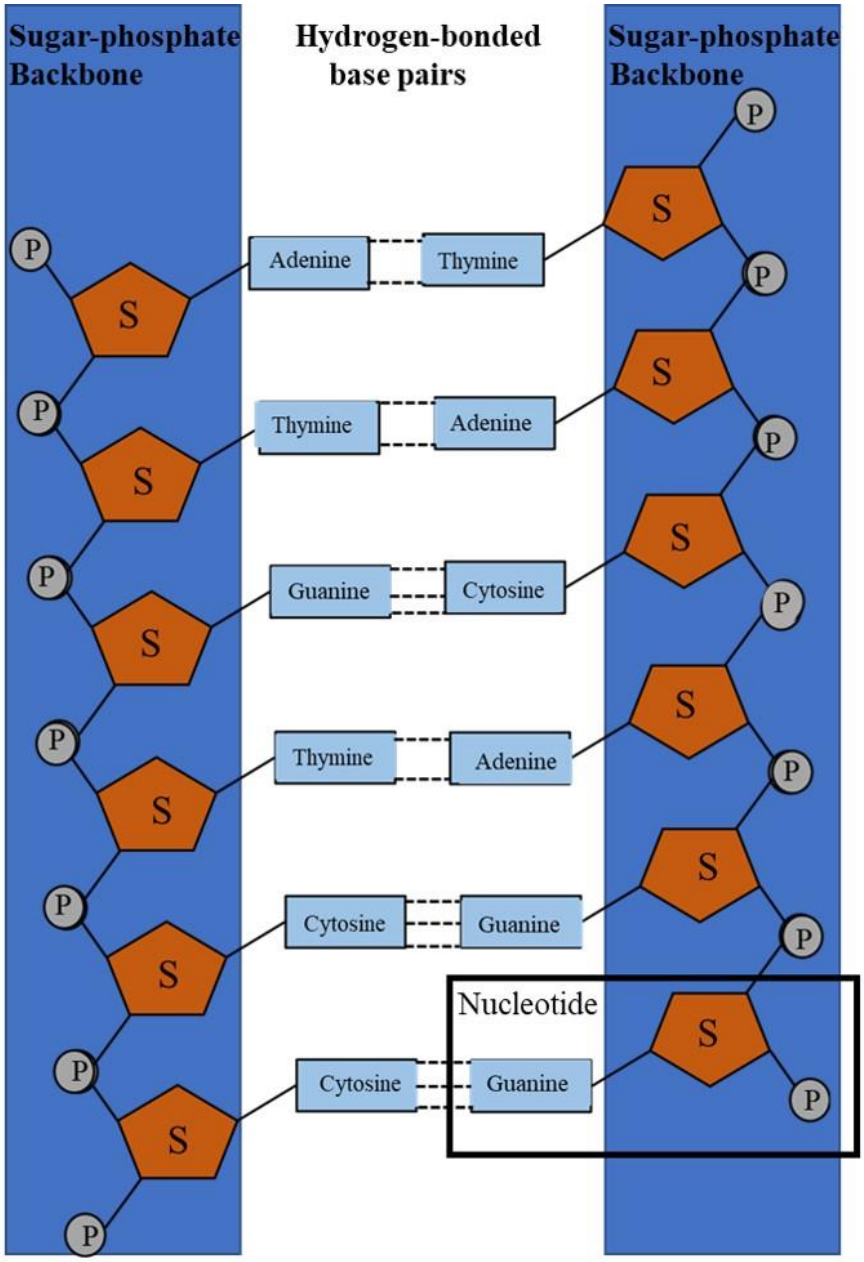
These sugar molecules compose the backbone of the DNA molecule and significantly contribute to its stability. There are archaeological examples of DNA molecules remaining intact for more than 8000 years.

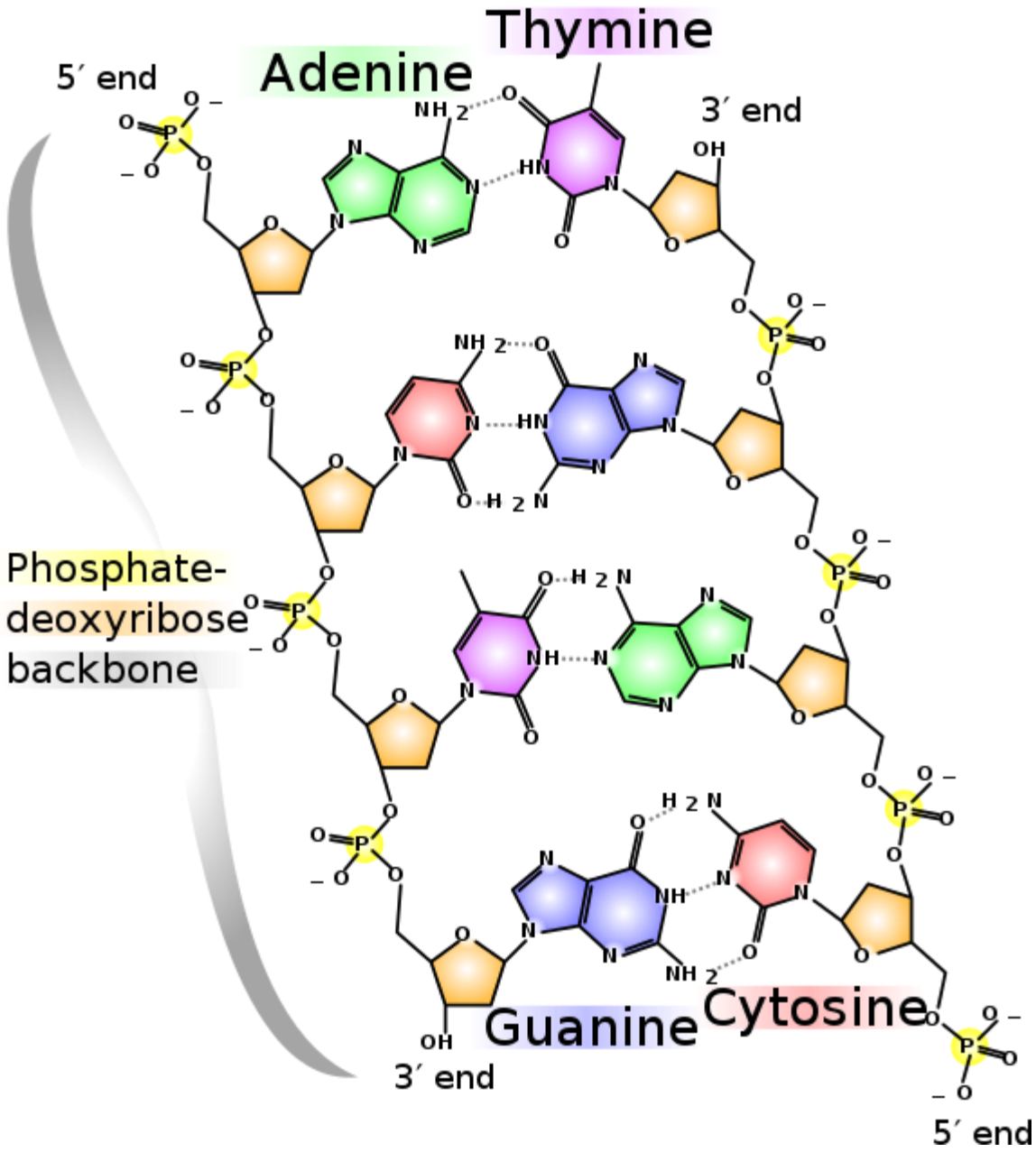
B. The Deoxyribonucleic Acid Molecule (DNA)

This drawing displays the DNA molecule in a strikingly geometric configuration. In reality the lateral blue rectangles on either side are curved in a double helical configuration. The sugar deoxyribose molecules, on either side, are arranged in a parallel fashion and joined together by phosphate groups forming the backbone of the molecule.

Here we have a color coded but otherwise, standard chemical structure displayed. It should be noted that the strands are positioned in opposite directions, antiparallel, as indicated by the five prime (5’) ends and the three prime (3’) ends of the sugar molecules. A hydroxyl group is located at the 3’ end, whereas a phosphate group is located at the 5’ end, each with their

characteristically different chemical properties. The chemical processes associated with DNA are direction specific, moving from 5’ to 3’.





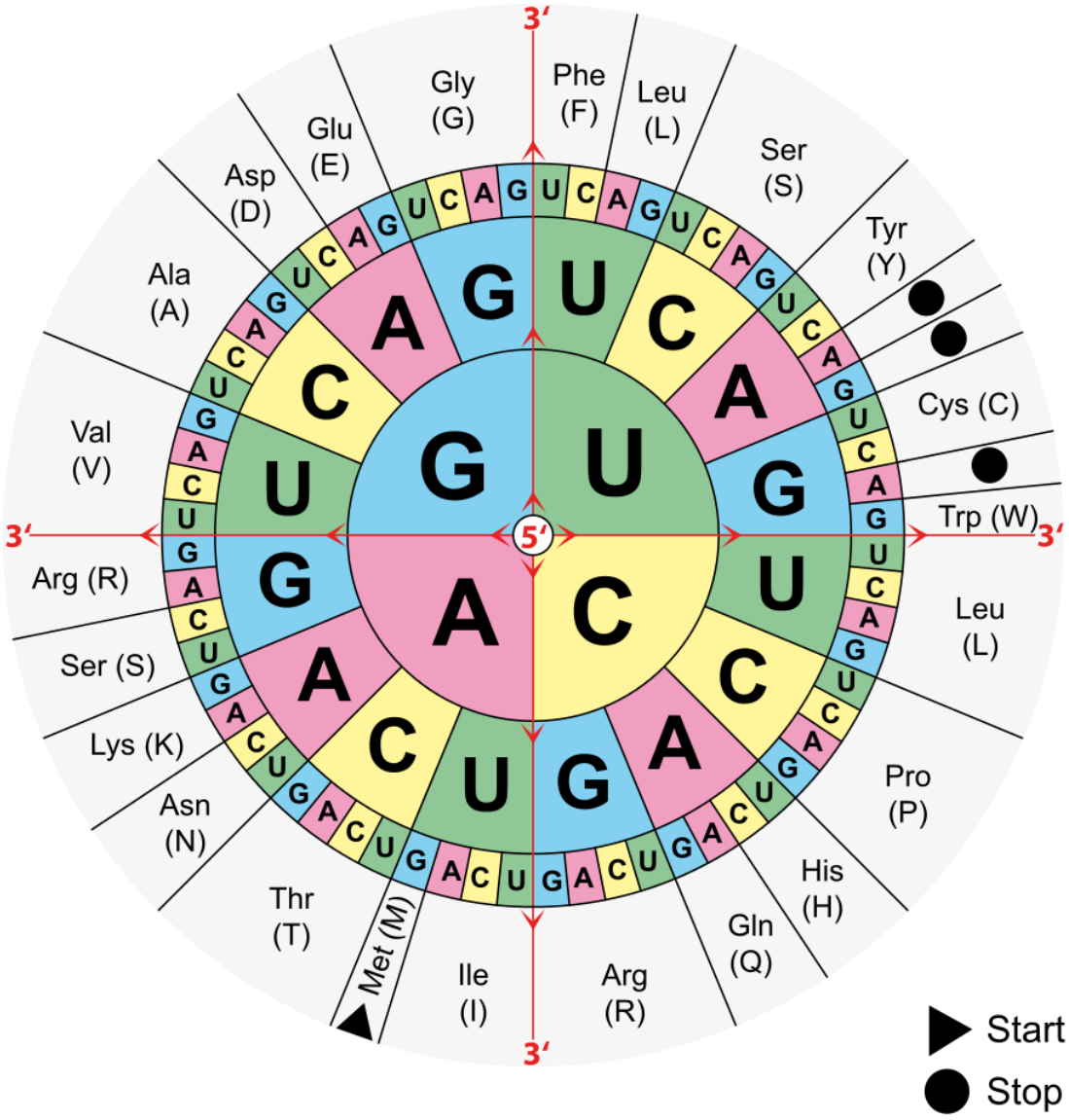
Chemical Structure Of Dna – Dna[sic] Molecule Structure Model. Used with permission from https://www.pngkey.com/maxpic/u2y3q8t4w7i1t4y3/

The DNA molecule is an information storage molecule. It stores all the information required to build and maintain a complicated multi-cellular organism such as a human being. The information is encoded in the DNA molecule based on the sequential arrangement of the nucleotides along the DNA strand, in which each group of three consecutive nucleotides spells a three-letter word known as a codon. There are four different nucleotides, adenine, thymine, cytosine, and guanine, in which the first letter of their name, A, T, C, and G, is used to spell the codon they represent. Since there

are four letters and each word is three letters in length, the total number of words encoded in the DNA molecule is 64, according to the mathematical expression, $4^3 = 64$.

This provides redundancy in that most of the 20 amino acids are indicated by several different names, (codons) in addition to a single codon indicating start and three codons indicating stop, UAA, UAG, and UGA, for each gene. All proteins start with the amino acid methionine. The codon for methionine, AUG, is also the start signal for all genes.

It is most remarkable that the genetic code is standardized for the entire living genome, applying equally to all living creatures starting with single cell organisms, yeasts, plants, aquatic animals, extending up through the phyla hierarchy to include human beings. This is known as the **Universal Genetic Code**.



The above diagram is designed to easily interpret and translate the **Universal Genetic Code.** By finding the first letter of the codon in the inner most circle, the second letter in the next concentric circle, and the third letter in the third concentric circle, one can identify the amino acid designated by that codon in the outermost circle. The **Universal Genetic Code** applies to almost all living organisms. The rare exceptions are in mitochondria, ciliated protozoans, and in a single celled plant known as *Acetabularia*.[2]

These exceptions are almost entirely due to past misreading errors of the stop codons as an amino acid and are not due to a change in the interpretation of the code which would involve exchanging one amino acid for another. There is no indication that significant changes, editing, or revisions of the **Universal Genetic Code** have occurred since the single celled organism at the beginning of evolutionary history.

The mitochondrial genetic code is much less well understood. There is some sharing of codons between the two codes.

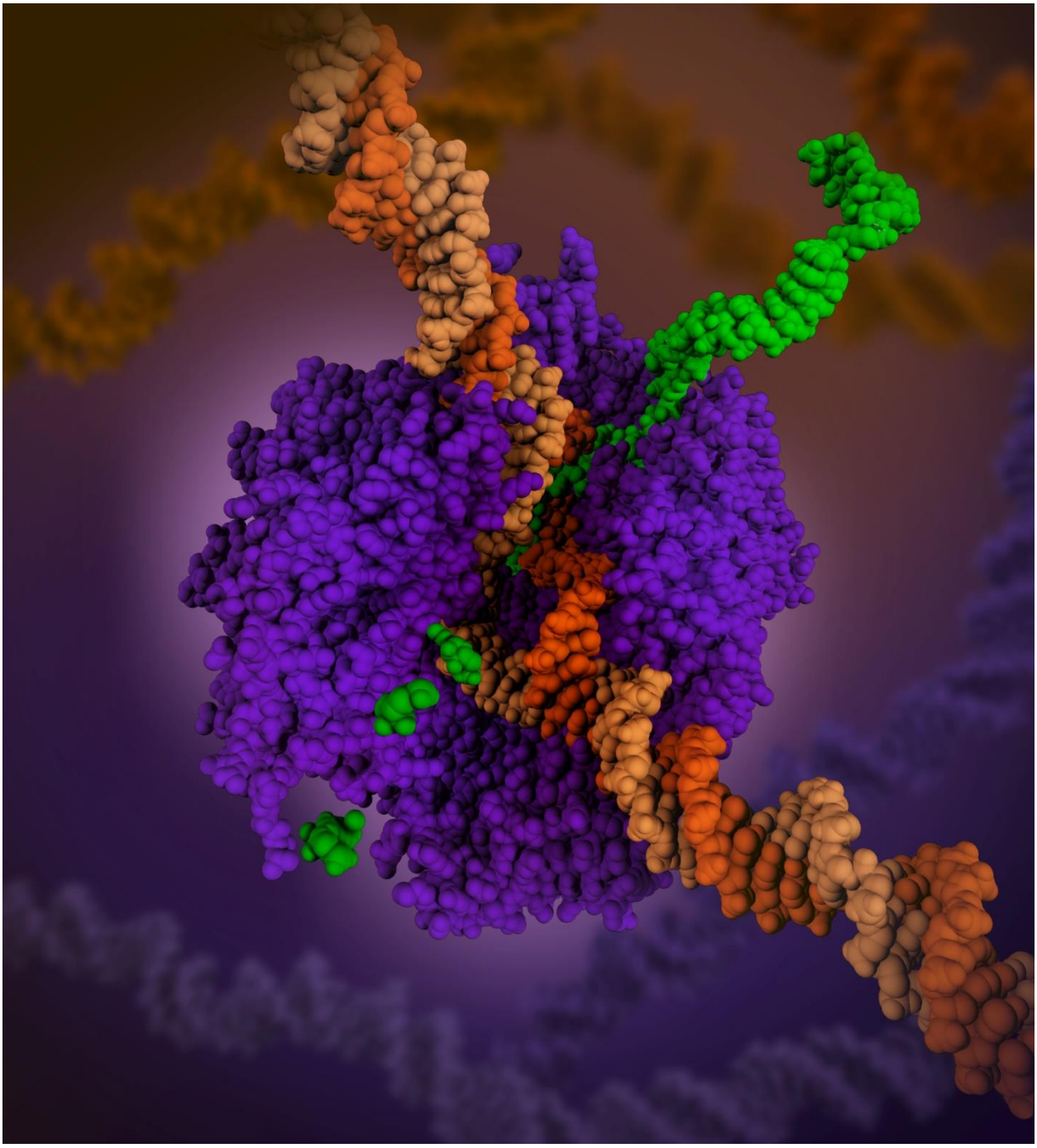
Life started with a reliable universal system capable of interpretating the blueprints for life as encoded and stored in DNA molecules. This appears to have been functional at the beginning of evolutionary history and has proven consistently capable of directing the building of the myriads of body parts. It is shared by the 8.7 million[3] different species presently living on earth, as well as the extinct species estimated to represent 99%[4] of all species that have ever lived on earth. Furthermore, epigenetics effectively directs and controls these genetic blueprints and how they are expressed within cells. It gives one pause to contemplate the dilemma of how such an elaborate system could be in place since the very beginning.

The astronomically small probability that an information bearing molecule as complex, large, unique, and stable as DNA could possibly emerge spontaneously with any imaginable combination of circumstances or conditions available on early earth apparently impressed Francis Crick to the degree that he wrote a scientific paper as well as personally proposed another worldly source of DNA based on the hypothesis of "Panspermia." He made an appearance at a conference organized by Carl Sagan in 1971 to promote this idea.[5]

"…[W]e organized and initiated the original life patterns of this world and planted them in the hospitable waters of the realm. All planetary life… had its origin in our three original, identical, and simultaneous marine-life implantations.[6]

"*450,000,000* years ago, the *transition from vegetable to animal life* occurred. This metamorphosis took place in the shallow waters of the sheltered tropic bays and lagoons of the extensive shore lines of the separating continents. And this development, all of which was inherent in the original life patterns, came about gradually. There were many transitional stages between the early primitive vegetable forms of life and the later well-defined animal organisms. Even today the transition slime molds persist, and they can hardly be classified either as plants or as animals." [7]

C. RNA polymerase II during active transcription mode of a DNA gene.



Maria Voigt and PDB-101 CC-BY-4.0, via Wikimedia Commons

Here we see the RNA polymerase II, colored purple, during transcription. The double stranded DNA is held in position by the jaws of the RNA polymerase in which the two strands, the bright orange and yellow orange,

have been separated. The sense strand, bright orange, is actively being transcribed, that is, copied onto a single strand of RNA, green. Following further modification, it will become a mature messenger RNA (mRNA) molecule. Note the background surrounding out-of-focus strands of DNA, in the typical coiled configuration when stored as chromatin in the cell nucleus where this process is taking place.

When released, the RNA strand will undergo further modification in the nucleus. The matured mRNA will then travel from the nucleus to the ribosome, located in the cytoplasm, where the information it carries will be translated and amino acid molecules will be assembled in precise sequence, producing a new protein molecule.

This entire process, the synthesis of the building blocks that compose an entire living organism, is known as **The Central Dogma of Molecular Biology**, simply stated as: "DNA to RNA to protein." We now know that, profoundly simplistic as this concept is, it does not begin to reflect the true complexity of the host of interacting factors controlling protein synthesis. It has been modified as follows: "Nucleic acids function as the 'brains and central nervous system' of the cell while proteins carry out the functions they specify," [8] referring to the large number of controlling actions performed by the epigenome. This concept will be discussed further in conjunction with our rapidly expanding recognition of the epigenetic significance of non-coding RNA genes (ncRNA) especially long non-coding RNA (lncRNA) of 200 or more base pairs in length.

D. History of Epigenetics

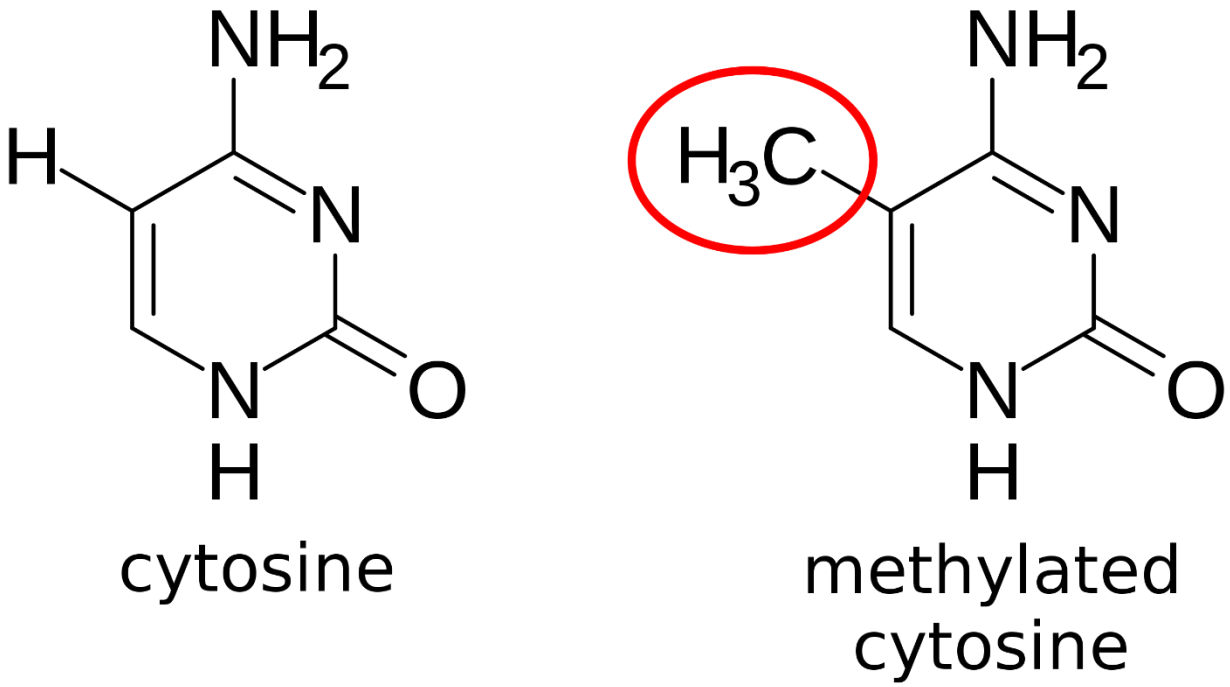
The epigenetic significance of methylation as a method of controlling the expression of genes was first recognized in 1979 by J. D. McGhee and G. D. Ginder.[9]

They compared the methylation status of the beta-globin locus in cells which invariably express the gene. They discovered that cells of un-methylated genes displayed active expression of the gene, whereas the methylated cells of did not. It was recognized that cell differentiation was linked to active gene expression and could therefore be used as an indirect indicator of the presence or absence of methylation of a specific gene. It is now widely recognized that as a result of methylation, 5-methylcystocine, produced by DNA methyltransferase enzymes (DNMTs), is widespread throughout mammalian genomes.

III. The commonly utilized epigenetic metabolic pathways are:

- Methylation
- Histone modification, acetylation and methylation
- Long non-coding RNA (lncRNA) mediated transcription regulation
- Phosphorylation
- Ubiquitination

A. Characteristics of DNA methylation



Methylation is the process of adding a methyl group to a given chemical moiety. In the case of epigenetics, it is usually added to the nucleotide cytosine at C5 position in the DNA molecule. A methyl group consists of one carbon atom and three hydrogen atoms [CH_3].

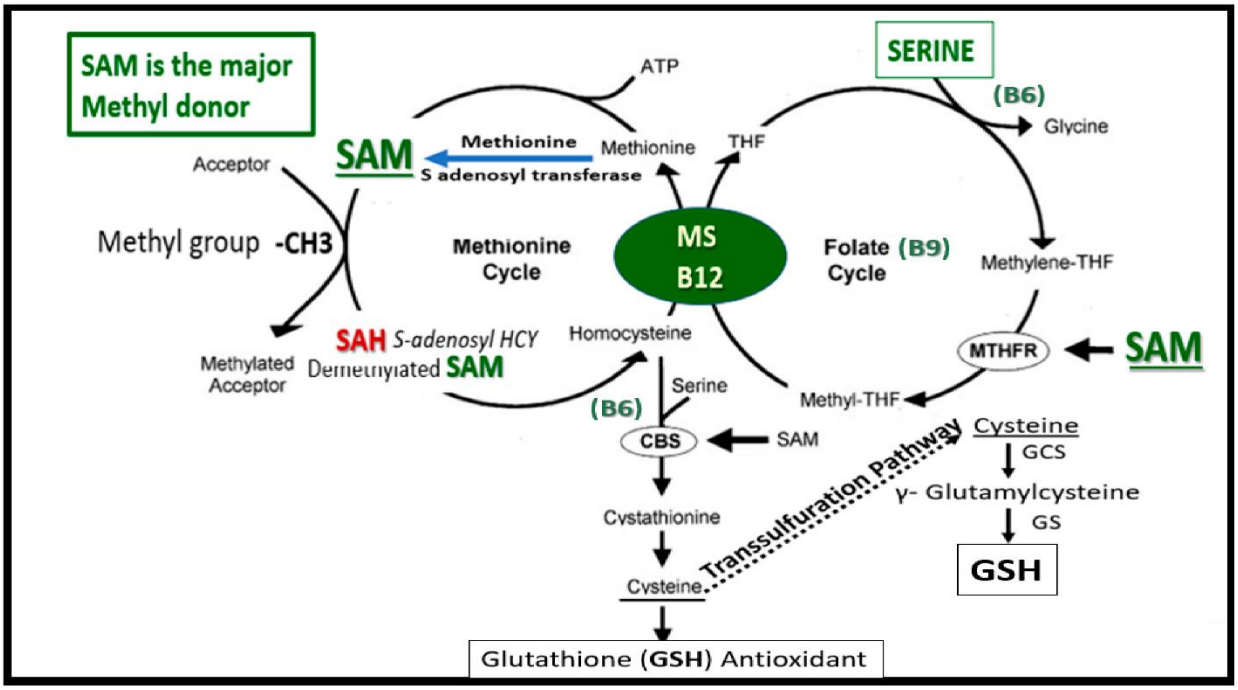
The standard chemical structures of cytosine display the unmethylated molecule on the left. On the right, a methylated cytosine molecule is displayed. The added methyl group, [CH_3], is encircled by red at the C5 position of the pyrimidine ring.

B. Essential Functions of Folic Acid or Its Conjugates:

- Production of red blood cells
- Producing DNA (purines and pyrimidines)
- Repairing DNA
- One-carbon methylation, the major source for the major molecular pathway of epigenetics.

Folic acid is an essential vitamin belonging to the B-complex group. By far the most common cause of folate deficiency is excessive alcohol intake. Alcohol decreases absorption of folate by the gastrointestinal (GI) track and at the same time increases clearance of folates through the kidneys, both contributing to folate deficiency. Other causes of reduced GI absorption of folate include, Crohn's disease, celiac disease, cancerous tumors particularly of the GI tract, and kidney dysfunction requiring dialysis.

One-carbon folate mediated metabolism is the major metabolic pathway for methylation in epigenetics.



Hayden, Marvin R. and Tyagi, Suresh C. CC-by-4.0 <http://creativecommons.org/licenses/by-sa/4.0/> via Medicina (Dec.23, 2021) vol. 58(1),16

The green box in the left upper corner announces the main function of folate mediated metabolism which is supplying S-adenosyl-methionine (SAM) with the methyl groups required for DNA methylation. In fact, it is the major methyl donor in the body, and since methylation is a major metabolic pathway for epigenetics, it is essential for epigenetic processes.

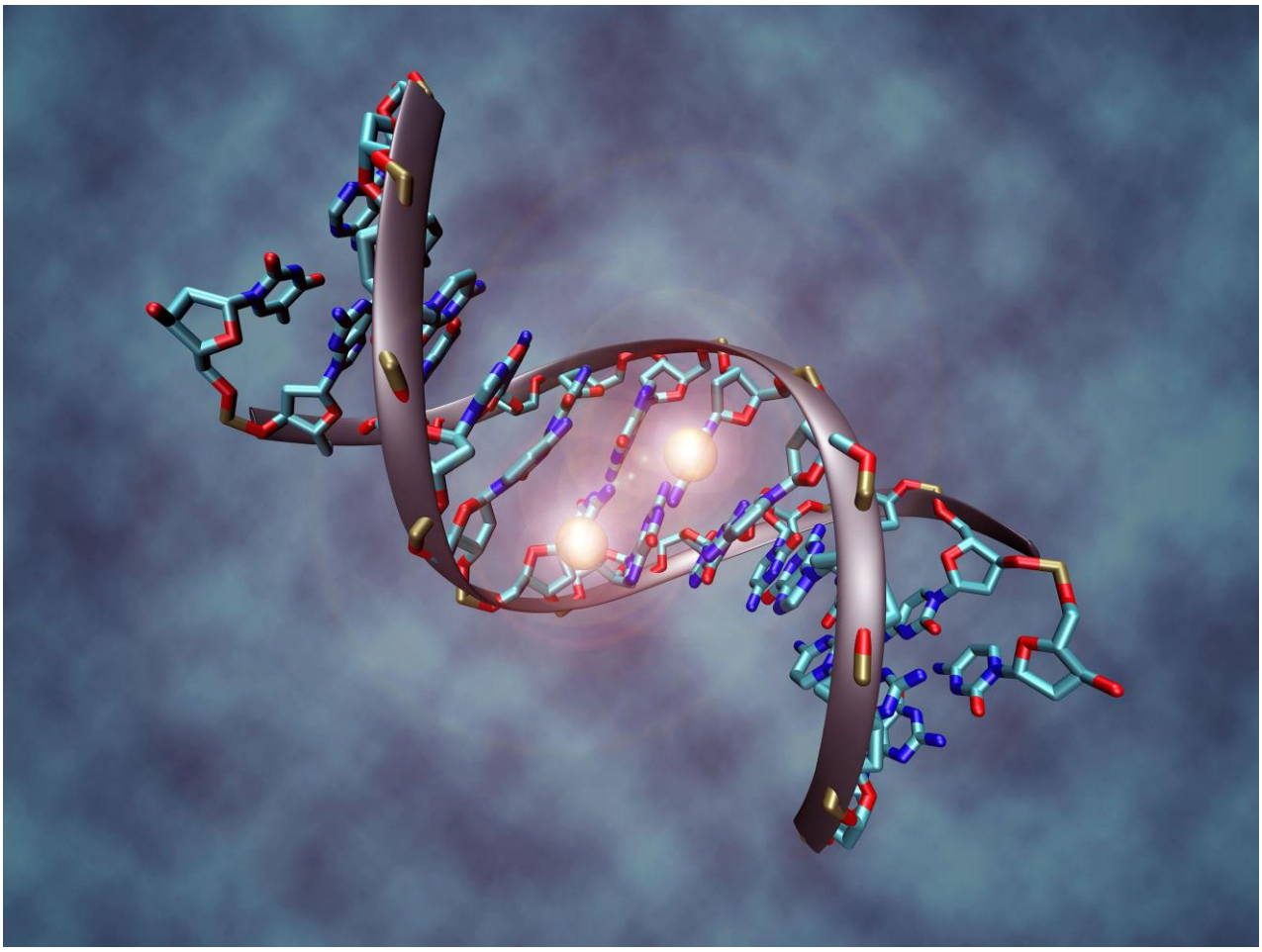
Illustrated here are two associated metabolic cyclical processes that are closely intertwined, the folate cycle and methionine cycle. Note the green oval joining the two cycles consisting of the enzyme methionine synthase labeled MS and the essential cofactor vitamin B12 participating in both cycles indicating how both pathways are joined.

Dietary folic acid is the main source of folates and folate conjugates. They undergo a folate enhancement process, requiring vitamin B3 as a cofactor, in which dihydrofolate becomes tetrahydrofolate, after which it feeds into the folate cycle to participate in the methyl transfer process. Dietary intake is also the major source of methionine. *De novo* synthesis of purine and pyrimidine, both essential components of all nucleotides are additional important products of this process.[10]

In addition to donating the methyl groups for DNA methylation, it also provides for methylation of RNA, histones, other proteins, phospholipids, and other molecules.[11]

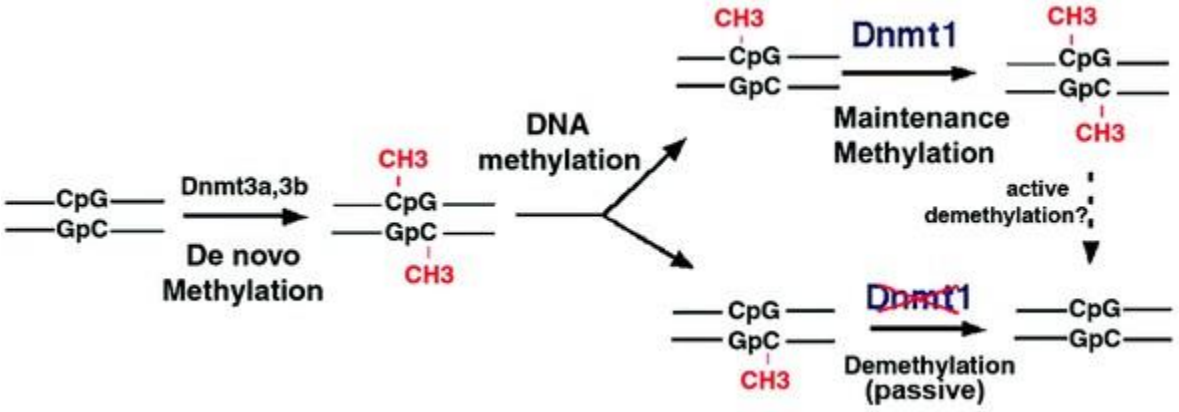
It becomes immediately apparent that a deficiency of folic acid or folate conjugates will result in significant alteration of cellular environments that could modify or block one-carbon metabolism. In this case the dietary environment represents a significant potential epigenetic factor.

C. An artistic rendition of a methylated short segment of DNA.



The colored image represents an artist's conception of two methylated cytosine nucleotides indicated by the two white balls, displayed in a short segment of the double stranded helical DNA molecule. It is not only an accurate display of the most common epigenetic chemical process; it is also a thing of beauty.

D. Illustration of *de novo* methylation versus maintenance methylation



Credit: Wu, Wao, and Sun, Yi Eve, Epigenetic Regulation of Stem Cell Differentiation, Pediatric Research, 59, p. 21 – 25 April 1, 2006

It should be noted that *de novo* and maintenance DNA methylation are different processes, requiring different DNA methyltransferases. *De novo* methylation is performed by enzymes DNMT3A and DNMT3B, whereas maintenance methylation is performed by DNMT1.

When a methylated strand of DNA is duplicated, maintenance methylation requires that additional methyl groups be added to the new strand opposite the previously *de novo* methylated sites of the original strand to maintain the same level and distribution of methylation. *De novo* methylation is particularly active during early embryonic development of organisms.[12]

E. CpG Islands are methylated in a non-random pattern.

Methylation of DNA is a conspicuous feature of vertebrate genomes in contrast to invertebrates. Antequera and Bird, reported that four percent of the total cytosines in vertebrates are methylated, representing about 5 x 10^7 5-methylcytosine (5 million cytosine residues) per diploid nucleus. Of interest is the fact that only 70 to 80 percent of the potentially methylatable sites are actually in a methylated state.[13]

A practical method of determining the distribution of methylation throughout a genome can be accomplished by staining cells with an immunofluorescent labeled antibody for 5-methylcytosine. These studies have shown that there is relatively low level but fairly uniform methylation of the CpG islands throughout mammalian genomes. In portions of the genome with relatively high concentrations of CpG islands, particularly in cancerous tumors, there

frequently is excessive methylation of normal suppressor genes, resulting in the silencing of genes that exercise a suppressive effect on tumor growth, thus favoring cancer growth and spread. This pattern of DNA methylation is referred to as *aberrant methylation* and known as *CpG Island methylator phenotype* (CIMP). This characteristic phenomenon of tumors is widely recognized and under intense investigation.

F. CpG islands

Interspersed non-methylated DNA sequences of approximately 1000 nucleotide base pairs in length are a conspicuous feature of CpG islands. These overlap promoter regions of 60 to 70% of all human genes, representing a significant potential for control of genetic activity.[14]

The distribution pattern of CpG islands throughout the genome remains an intriguing and puzzling issue. They are definitely distributed in a non-random fashion. The degree of methylation of the CpG islands is also strikingly non-random. The bulk of 5-methylcytosine is distributed outside the areas known as CpG islands which are largely unmethylated. These are frequently located in the promotor region of housekeeping genes. (The term housekeeping genes refers to genes that control the production of common proteins required by essentially all cells. They usually produce relatively small incremental amounts of protein but do so on a regular basis.) Since these cytosine base pairs are largely nonmethylated their associated genes remain normally expressive. This is paradoxical when one considers that the CpG islands contain relatively concentrated substrate for action by DNMTs.

In reference to this situation, Paola Caiafa stated, "How the CpG moieties in CpG islands become vulnerable or resistant to the action of DNA methyltransferases and can thus lose or maintain their characteristic pattern of methylation is still an open question. Our aim is to gather some mechanisms regarding this intriguing enigma, which, despite all energy spent, still remains an unresolved puzzle." [15]

As a scientist, one must frequently reach beyond the simple scientific method in an attempt to understand scientific data. There are sources of information which are nonscientific but nonetheless provide clear explanatory information as follows:

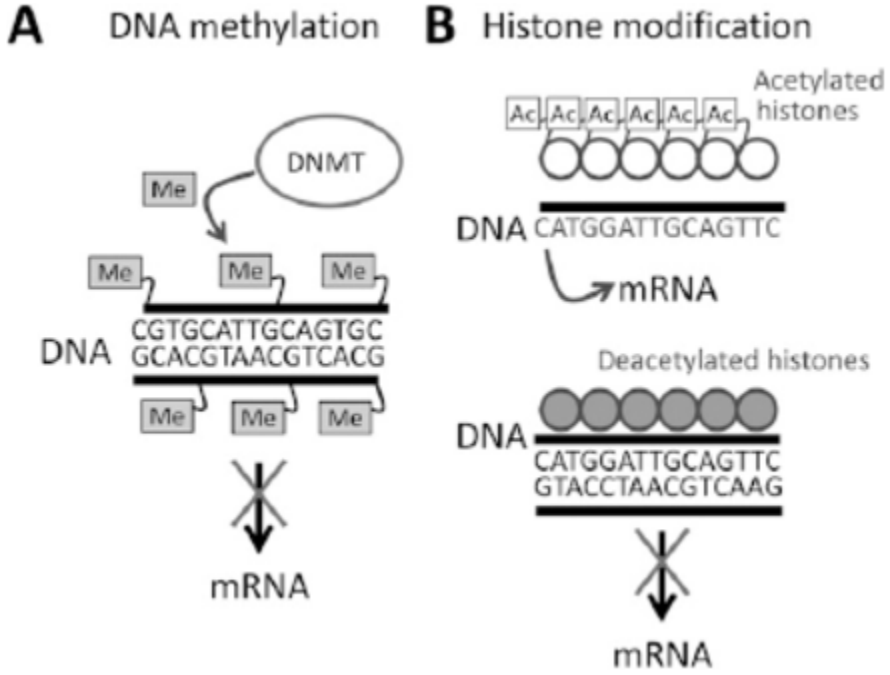
"And yet some of the less imaginative of your mortal mechanists insist on viewing material creation and human evolution as an accident." Furthermore, the authors, "…have assembled over fifty thousand facts of physics and chemistry which they deem to be incompatible with the laws of

accidental chance, and which they contend unmistakably demonstrate the presence of intelligent purpose in the material creation." [16.]

An explanation of the puzzling molecular behavior that confronts us by the unpredictability of 5-methylcytosine transferases certainly appears to be *"incompatible with laws of accidental chance."* The grossly non-uniform distribution of CpG islands throughout the mammalian genome is similarly inconsistent with simple probability.

More compelling that nonmechanical factors are at work is the example of preplanning, requiring intellectual processes, including reasoning, encoding, and translation, exemplified by the **Universal Genetic Code**. The very existence of information encoded by the three consecutive base pairs in codons, that can then be shared with mRNA through the process of transcription in which the information is passed on to the ribosome where it is translated in order to produce thousands of specific proteins, clearly begs the question, how could it have occurred without intelligent preplanning and supervision?

G. DNA methylation and histone modification



Credit: Gudsnuk K, Champagne FA. Epigenetic influence of stress and the social environment. ILAR Journal. 2012;53(3-4):279-288.

This schematic drawing illustrates the combined processes of DNA methylation and histone modification. The processes involving methylation of the cytosine and acetylation of histones affect each other in a variety of

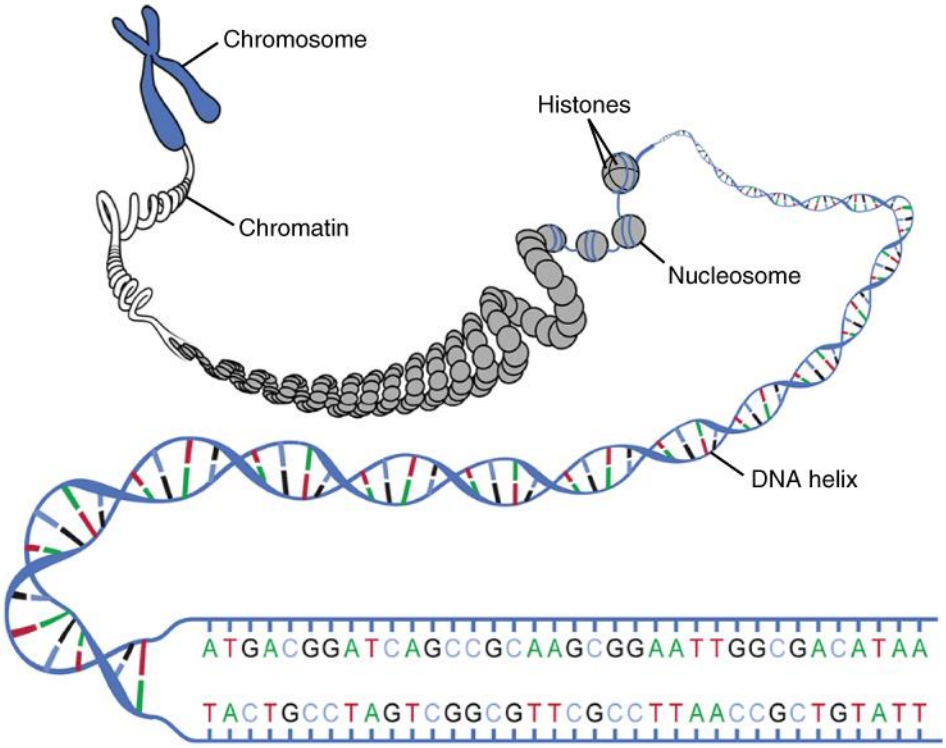
ways. On the left, (A), DNA methylation is a process in which methyl groups (Me) are added to cytosines in DNA by the enzymatic activity of DNA methyltransferases (DNMTs). The attached methyl groups interfere with transcription initiation resulting in turning genes off.

On the right, (B), the top row, acetylated histones, indicated by the presence of acetyl groups (Ac) on histone proteins resulting in reduction of electrical attraction between them, causing loosening of the DNA strands. The acetyl group is added to the amino acid, lysine, located in H3, or less frequency frequently H4. These are two of four paired histones that compose an octamer, also known as a nucleosome. Deacetylation causes the strand to be more compactly wound, thus making it less assessable for active gene expression. This is illustrated by the open circles representing nucleosomes. In contrast, on the bottom, reversal of the above process, or deacetylation, reverses the process, effectively blocking transcription by mRNA, signified by the filled in nucleosome circles.

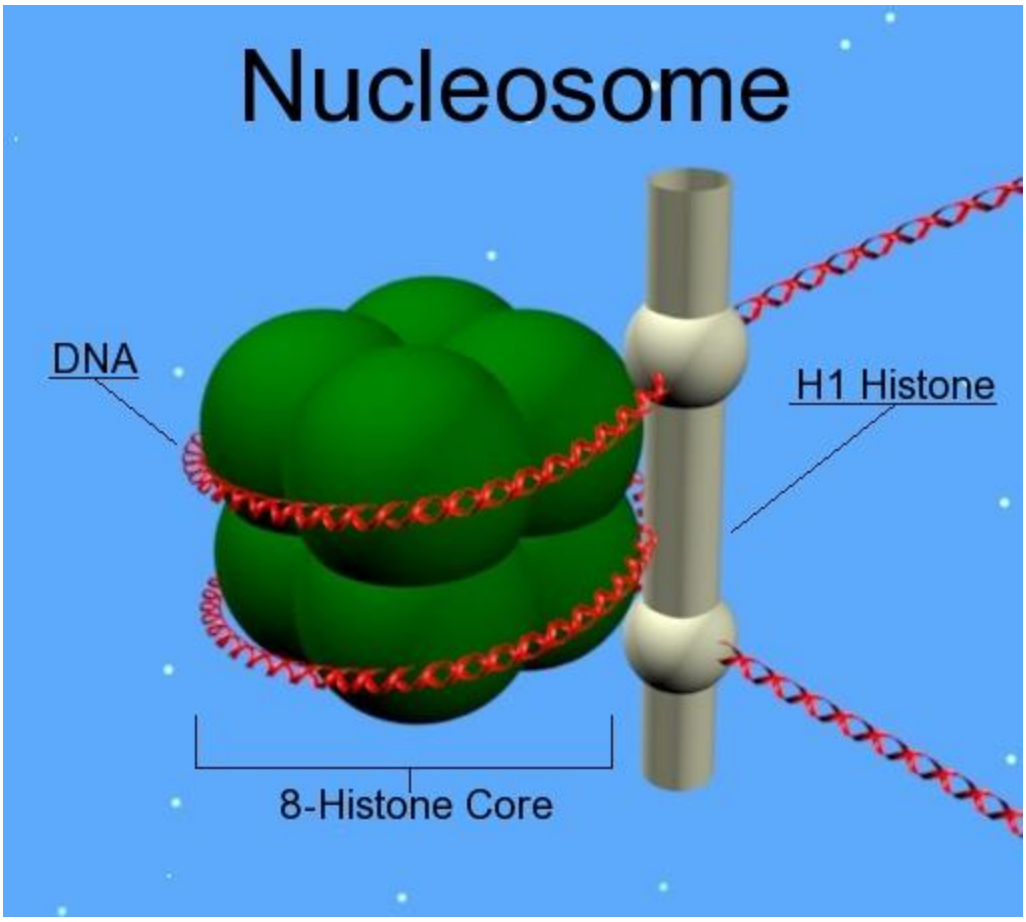
H. Storage and retrieval of DNA

When one considers the gigantic length of the DNA molecule, averaging 1.8 meters per individual cell, stored entirely within the nucleus, two microns in diameter, in a manner that allows copying of the approximately 23,000 genes at all times, it is not surprising that an elaborate storage and retrieval system must be in place. The nucleosome is spool shaped providing a compact means for storing DNA strands in the nucleus. There are one and two-thirds turns of the DNA strand on each nucleosome, containing 147 base pairs. Nucleosomes undergo extensive further coiling and compaction when stored as chromatin.

Histones H3 and H4 undergo the majority of these modifications, although histones H2A and H2B also are subject to some alterations. The enzymes that catalyze these changes are diverse, and include histone methyltransferases (HMTs), and histone acetylases (HATs) among others. These changes, on the other hand, are reversible and specific enzymes catalyze their removal. For instance, histone demethylases (HDMTs) and histone deacetylases (HDACs) catalyze the removal of the methylation and acetylation marks in histones, respectively. Besides post-translational modifications at the histones N-terminal tails, the core domains of the histones also undergo modifications.



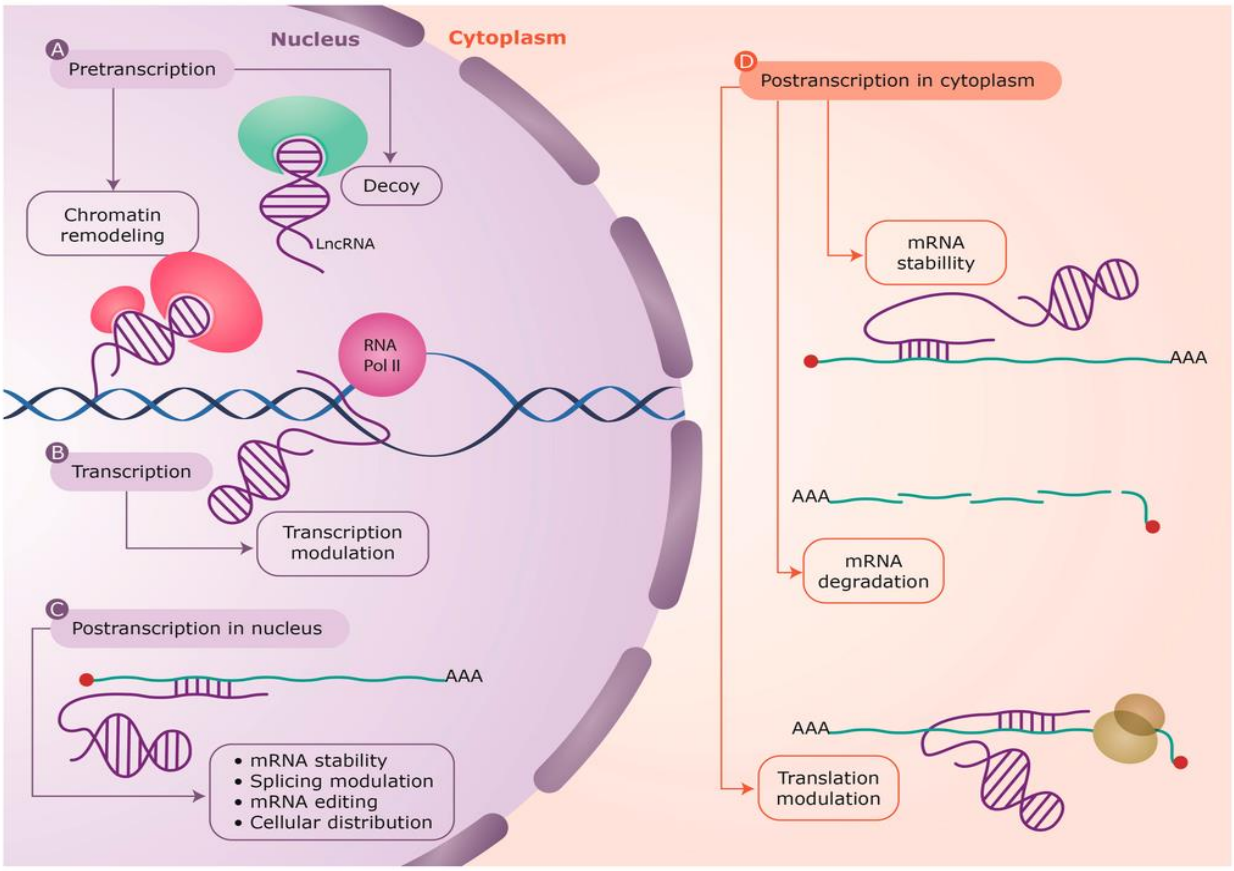
This image displays a composite of the various phases of DNA molecules beginning with a chromosome in the left upper corner and extending through the chromatin or storage phase, then the histone and nucleosome phase, next the transcription phase, and finally the two parallel uncoiled and unzipped DNA strands, showing DNA in its most accessible state. Which of these phases the DNA is in is almost entirely controlled by epigenetics, particularly histone modification by acetylation and methylation.



(Wikipedia, public domain) The average amount of DNA stored in each of the 10+ trillion cells in a human body contains approximately 3.3 billion base pairs, the DNA strands measure 1.8 meters in length which is folded and compacted in the form of chromatin that fits into the cell nucleus measuring two microns in diameter.[17]

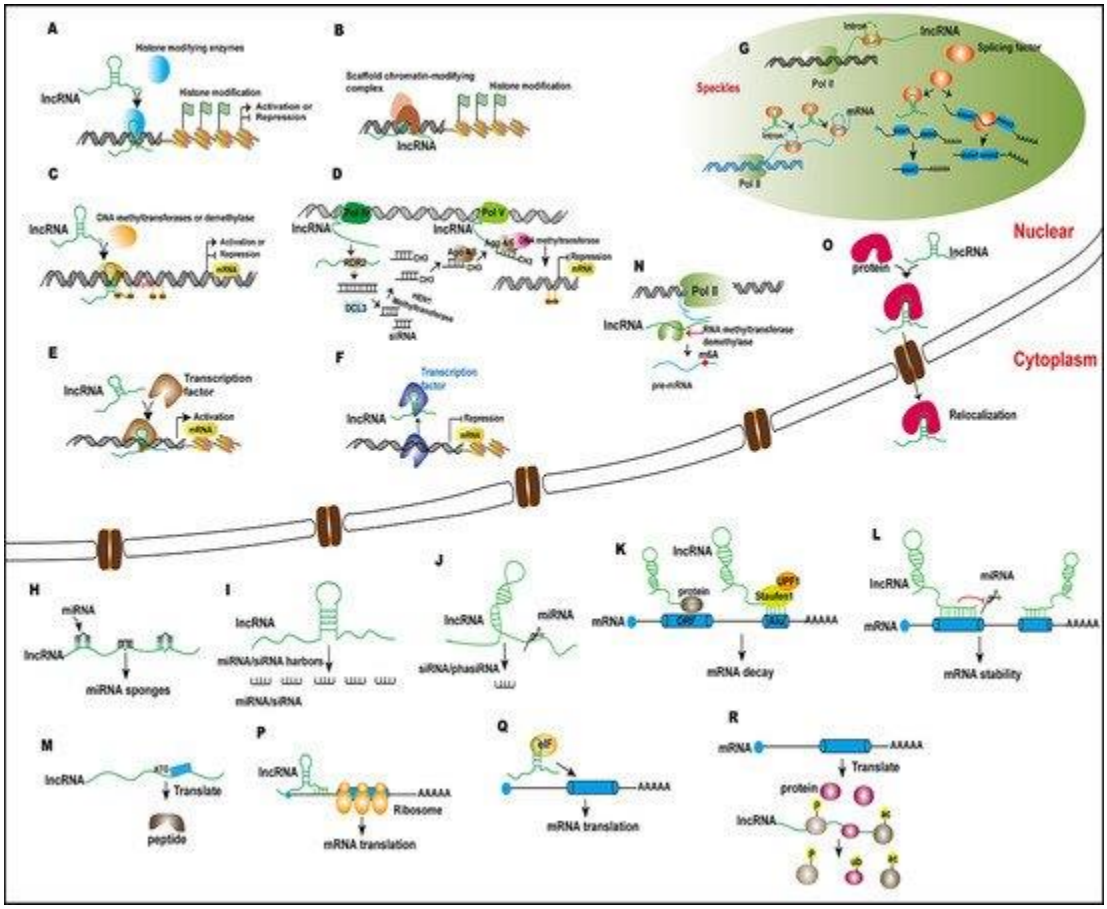
Several medical drugs have been developed which counteract specific disease-causing epigenetic effects. Examples are 5-azacytidine and 5-aza2′deoxycytidine. The biochemical action for both drugs is based on their ability to be incorporated into the DNA molecule in place of cytosine. Once there, they are capable of blocking DNMT enzymes, inhibiting DNA transcription.[18]

J. Antisense lncRNAs have been found to act at nearly every level of gene regulation.



Credit: Villegas, Victoria E., Zaphiropoulos, Peter G., CC-BY-4.0 via Neighboring Gene Regulation by Antisenes Long Non-Coding RNAs, International Journal of Molecular Science, (February 3, 2015), 16(2) 3251-3266.

Long non-coding RNA have been found to act at nearly every level of gene regulation, including the three major phases of transcription: pre-transcription, transcription, and post-transcription. It acts as a decoy in which a lncRNA attaches to a protein molecule involved in initiating transcription, thus preventing gene function. During transcription it can interfere directly by transcription modulation again preventing the gene from being expressed. During post transcription it can interfere with mRNA stability, with splicing modulation, with editing of mRNA, and in cellular distribution. The activities mentioned above all occur within the cell nucleus. Additional activity in the cytoplasm includes interfering with mRNA stability, causing mRNA degradation, and interfering with translational activities at the level of the ribosome.[19]



Credit: Zhang, Xiaopei et al. CC-BY-4.0 via "Mechanisms and Functions of Long Non-Coding RNAs at Multiple Regulatory Levels." International journal of molecular sciences vol. 20,22 5573. 8 Nov. 2019

K. A list of regulatory mechanisms expressed by lncRNAs thus far identified among the tens of thousands that are now known.

This very busy slide is an attempt to display the well documented recognized epigenetic actions of lncRNA genes of which tens of thousands have been identified in which the functions of many remain to be delineated.
"(**A**) lncRNAs interact with histone-modifying enzymes to activate or repress gene transcription. (**B**) lncRNAs recruit histone-modified complexes or act as scaffolds for multiple histone modifiers to regulate histone modification of genes and thereby regulate gene transcription. (**C**) lncRNAs recruit DNA methyltransferases or demethylases to regulate the target gene transcription. (**D**) Pol IV/V transcribed lncRNAs are involved in RNA-dependent DNA methylation, thus activating or repressing gene transcription. (**E**,**F**) lncRNAs interact with transcription factors to activate or repress gene expression. (**G**) lncRNAs interact with splicing factors or

proteins to regulate the mRNA alternative splicing; splicing factors directly regulate the lncRNA's alternative splicing in speckles. (**H**) lncRNAs act as miRNA sponges that regulate target gene expression. (**I**) lncRNAs act as miRNA or small interfering RNAs (siRNA) precursors. (**J**) miRNAs target lncRNAs to produce siRNA or phased small-interfering RNAs (phasiRNAs). (**K**) lncRNAs are involved in the Staufen1-mediated mRNA decay, and lncRNAs bind to proteins and mediate mRNA decay. (**L**) lncRNAs directly bind to mRNA and regulate mRNA stability, or competitively bind to mRNA to improve mRNA stability. (**M**) lncRNAs can be translated to peptides. (**N**) lncRNAs interact with RNA methyltransferases or demethylases and thus regulate mRNA expression. (**O**) lncRNAs combine with proteins to regulate protein localization. (**P**) lncRNAs interact with mRNAs and affect mRNA translation. (**Q**) lncRNAs bind the translation initiation complex eIF (eukaryotic initiation factor) to regulate mRNA translation. (**R**) lncRNAs interact with proteins and control protein phosphorylation, acetylation, and ubiquitination at the post-translation level."[20]

Only a few years ago non-coding genes were designated "junk" DNA.The protein coding portion occupies approximately 2% of the human genome. A large portion of the reminder, now estimated to be between 70 and 90%, is non-coding RNAs (ncRNAs). Long noncoding RNAs is a category consisting of more than 200 nucleotides in length and is of particular interest to geneticists at present.

The role of lncRNA in cancer diagnosis and treatment has mushroomed in recent years. The relative importance of the genome has dramatically shifted in favor of the non-coding portion both in terms of its massiveness and its functional significance. Perhaps it is time to acknowledge that protein coding genes should be removed from the pedestal upon which they have been placed by the central dogma and replaced by the new reality in which the non-coding RNA genes are given their rightful place. An appropriate revision would read: "Non-coding RNA, as expressed through well-established epigenetic molecular pathways, controls the flow of genetic information from DNA to RNA to protein!"

L. Phosphorylation

Phosphorylation is an epigenetic reprogramming that occurs during the embryonic period which is the most dynamic growth period for any organism. This is when stem cells are being selected and directed along specific cell lines and organ development. The locations of the various organ systems are being established. The Hox genes are engaged in directing the

layout of the major body plans. It is now widely known that phosphorylation is involved with histone methyltransferases, functioning as "writers," "erasers," and "readers," that program the epigenome. The use of these literary terms in describing biological functions related to the interpretation and application of the Universal Genetic Code are used advisedly since we are in fact dealing with the most stable and reliable language known, having proven its efficacy during constant world-wide usage for more than 500 million years.[21]

M. Ubiquitination

Ubiquitination is a complex process involving a large group of proteins that are involved with controlling many protein processes and functions. Ubiquitin is composed of seven lysine residues enabling it to form many protein bonds. There are more than 200 different proteins in which interactions occur in humans. Ubiquitin readily forms chains resulting in multiubiquitination with many proteins. Its epigenetic functions include protein degradation, repair of damaged DNA, mRNA synthesis (transcription), defense against pathogens, is involved in cell division and cell cycle progression, intracellular trafficking of proteins, and programmed cell death (apoptosis).[22]

IV. X-chromosome Inactivation, an Epigenetic Procedure, Essential for Viability of All Female Mammals.

Credit: Michael Bodega (public domain)

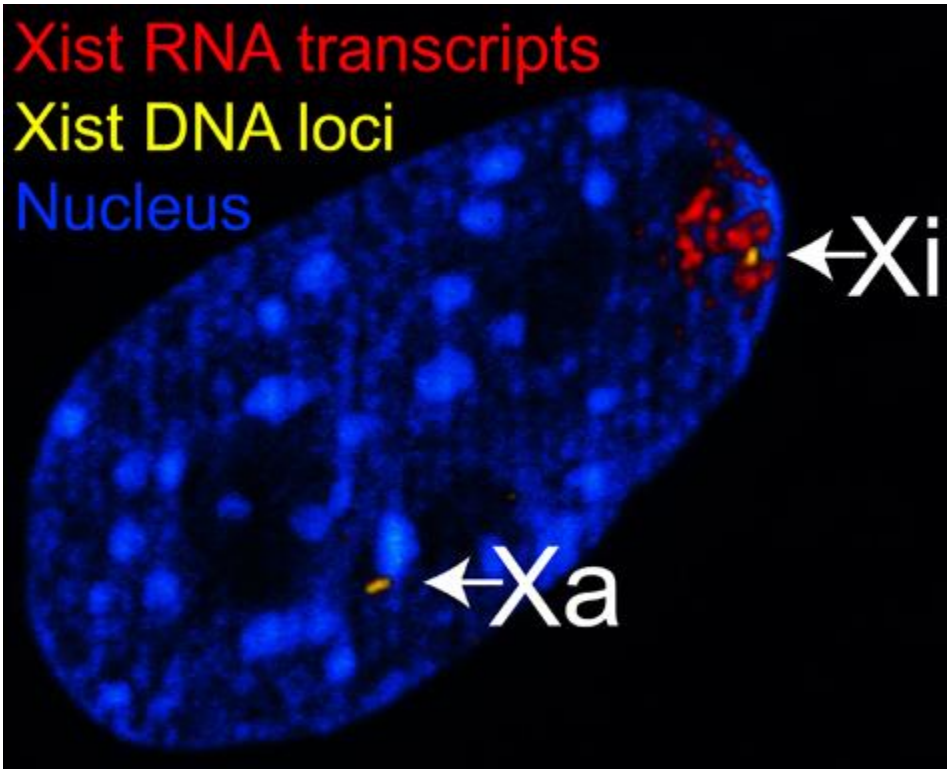
A. The tortoiseshell cat

The tortoiseshell cat pictured above is an excellent example of the two distinctive coat colors that are frequently present in female furbearing mammals. They represent the varied, random display of either one or the other allele inherited from the two parents in random areas of the animal's coat. Note the black fur composing most of the tail compared with the highly variegated display on much of the rest of the cat particularly the light area immediately above the tip of the tail.

An interesting phenomenon involving the alteration of fur color in many furbearing female mammals is a result of X-chromosome inactivation. In fact, it was the distinctive mottled fur color noted in laboratory mice that was recognized by Mary Lyon, a prominent geneticist, who was the first to appreciate its significance based on her knowledge of allele genes

responsible for determining the fur color of many mammals. She most astutely recognized that the mottled colored fur was the result of silencing a fur color allele, resulting from X-chromosome inactivation.

The X-chromosome inactivation process occurs during the first 6½ days following fertilization in humans. It occurs prior to intrauterine implantation and is complete by approximately the 30-90 cell zygote stage. X-chromosome inactivation occurs independently in each cell. The selection of whether the paternal X-chromosome or one of the two maternal X-chromosomes will be silenced, is random, and once that is determined in each of the approximately 90 zygote cells, each of their daughter cells will receive the same genome and pass it on. The result is a 50-50 chance that each fur producing cell will express the paternal allele and an equal chance, the maternal allele, hence the typical calico cat.

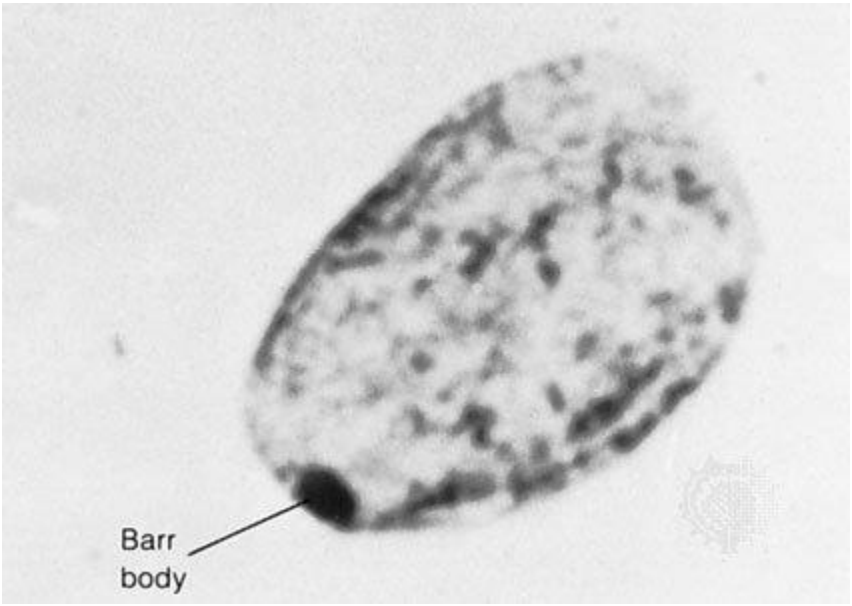


B. An experimental demonstration xist

The above image of a nucleus in a female mouse fibroblast cell is a confocal picture from a combined RNA-DNA FISH experiment for Xist. The female-

biased expression of long non-coding RNAs in domains that escape X-chromosome inactivation are indicated. The upper arrow (Xi) indicates Xist RNA transcripts (red fluorescent-stained areas) associated with the incompletely inactivated X-chromosome. The lower arrow (Xa) indicates the normal X-chromosome with a Xist DNA loci (yellow fluorescent stained).[23] (Xist is an RNA transcripter that is essential for X-chromosome inactivation.)

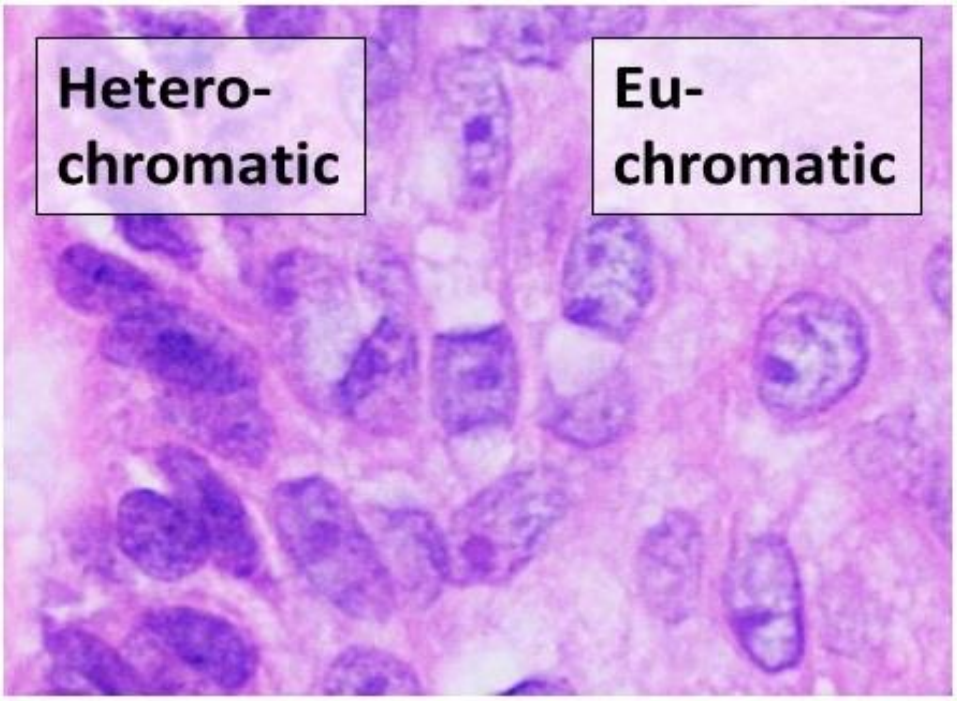
C. Barr Body in Nucleus



Credit: Cytogenetics Laboratory of Dr. Arthur Robinson, National Jewish Hospital and Research Center/National Asthma Center, Denver, Colorado

The Barr Body is an end-stage inactivated X-chromosome. It appears as a dense, dark-staining spot at the periphery of the nucleus of each somatic cell in the human female. It represents the end stage inactivated X-chromosome. It contains a large amount of heterochromatin, which is largely responsible for X-chromosome inactivation. Identification of the Barr Body is a common legally accepted confirmation of biological sex of women athletes.

D. Microscopy of heterochromatic versus euchromatic nuclei H&E *(hematoxylin and eosin)* stain



Credit: Mikael Häggström CC0 1.0 via Wikimedia Commons

This image displays marked crowding of nuclei in the heterochromatic tissue on the left in contrast to normal euchromatic nuclei on the right.

Deacetylation is associated with heterochromatin deposition which can permanently reduce gene expression and is a significant part of the process responsible for X-chromosome inactivation. X-chromosome inactivation is an essential process that occurs in the very early embryotic stages in all female mammals. *The female embryo otherwise would not survive.*
Heterochromatin rebalance addresses the otherwise marked imbalance caused by two X-chromosomes in a female, (XX) and only one in the male, (XY). Heterochromatin is deposited throughout the entire X-chromosome, essentially turning off the genes although a few apparently escape and remain functional. It is also widely distributed in normal chromosomes performing structural functions such as centromeres which is the central focal point in each chromosome during cell division.

V. The role of epigenetics in the etiology and treatment of cancer

There are six widely accepted cellular features in cancers. In 2000, Hanahan and Weinberg reported an analysis of the metabolic features of cancers. They recognized and described six characteristics or features of cancer which they called The Hallmarks of Cancer.[24] These are:

- self-sufficiency in growth signals
- insensitivity to anti-growth signals
- tissue invasion and metastasis
- limitless replicative potential
- sustained angiogenesis
- evasion of programed cell death (apoptosis)

A. LncRNAs are involved in all aspects of cancer metabolism.

LncRNAs have been found to impact essentially all aspects of tumor metabolism. We will start with their involvement in promoting the metastatic activity of cancers.

Hepatocellular carcinoma (HCC), (liver cancer) is generally one of the more aggressive tumors in humans. One of the six features of cancer described by Hanahan and Weinberg is its ability to metastasize to other parts of the body. In fact, the cause of death is usually due to metastases rather than the primary tumor. We will therefore consider the role of lncRNA in the metastatic processes on the molecular level.

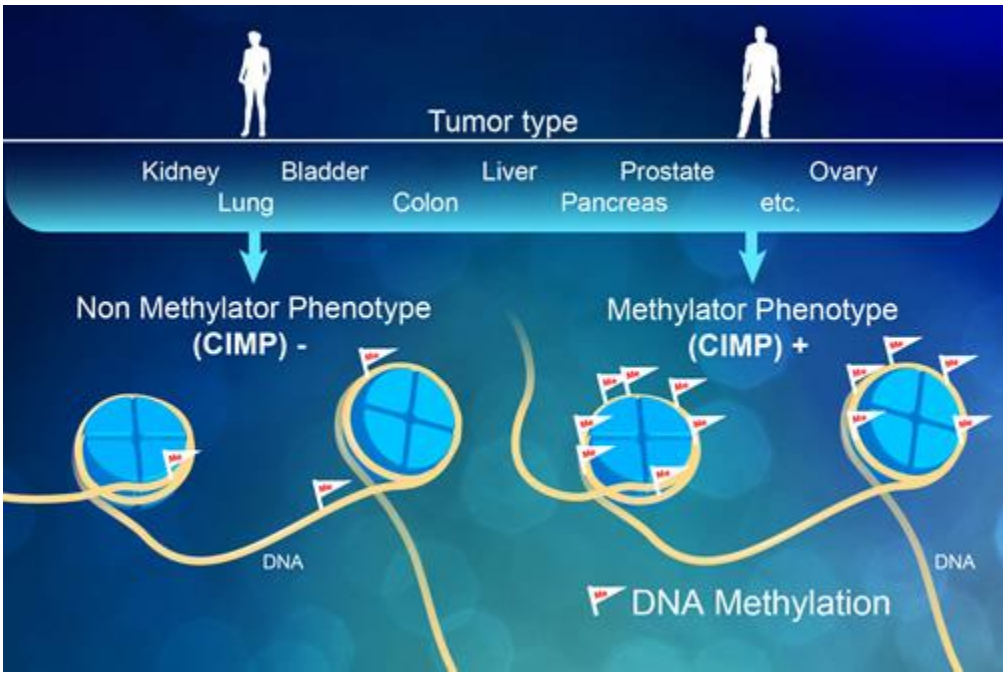
Transforming growth factor beta was found to induce the formation of a complex in which the growth factor combines with lncRNA to form the complex lncRNA-ATB, which in hepatocellular carcinoma facilitated the process, *epithelial to mesenchymal transition* (EMT), that results in cellular invasion and organ colonization by hepatocellular carcinoma cells by two distinct RNA – RNA interactions. The lncRNA-ATB complex competitively binds to miR – 200 that activates two other moieties that contribute to EMT to enhance a signaling process that promotes metastasis.[25]

This is a minimal simplistic sampling of the complexities involved in understanding the role of epigenetics in cancers at the molecular level. This applies to only one of the six major characteristics of cancer metabolism. A fairly comprehensive discussion of the role of lncRNAs in cancer is offered by

Adam M. Schmitt and Howard Y. Chang in a paper entitled: "Long Noncoding RNAs in Cancer Pathways," in *Epigenetics and Cancer*, April 2016, for those of you who are interested. In fact, there are many research papers based on the great deal of continuing investigation of this are subject.

B. CpG Island Methylator Phenotype (CIMP)+

In 1999 Toyota and colleagues recognized an important concept that occurs in many cancerous tumors known as, *CpG Island methylator phenotype* (CIMP)+[26]. This is a striking demonstration of the significant role of epigenetics in the occurrence of cancer including a number of its metabolic characteristics such as rapid growth rate and propensity to metastasize. It also provides clues to prognosis and guidance in selecting the most effective treatment. In fact, this has dramatically altered our approach to diagnosis and treatment of cancer in general. Up until about 35 years ago it was widely accepted that cancers were caused primarily by oncogenic mutations resulting in uncontrolled growth of abnormal cells. Recognition of CIMP+ has brought into clear focus the need for determining the associated epigenetic factors in order to adequately diagnose and treat cancers.



Credit: Nhgri CC-BY 2.0 via flickr

The transition from recognizing cancer as primarily an oncogenic disorder to the present where it is now recognized that the epigenome plays an

essential role, required about a decade. The diagnostic workup for treating cancer now routinely requires analysis of the CIMP+ status and the routine analysis of cancers such as colon carcinoma, breast cancer, and pancreatic cancer, generates a great deal of information, contributing immensely to our understanding of the complexities of CIMP+ features across the entire spectrum of cancerous tumors.[27, 28]

Included in the epigenetic analysis of malignancies is an analysis of the genes and genetic mutations causing and contributing to tumor growth. We are finding that many of the highly active genes during embryonic development are also associated with many cancers including the same genes in tumors of many different organs.[29]

V. Other important epigenetic functions

A. Transgenerational Epigenetics Occurs Via Imprinting and Epigenetic Reprogramming in Sperm and Embryos

High levels of methylation exist in the sperm during and following spermatogenesis as well as in the ovum prior to fertilization. During the fertilization process there is active, rapid, global demethylation of the sperm. Demethylation of the ovum occurs passively and slightly later, starting with the 2-cell zygote stage. Following the embryonic blastocyst stage, methylation of the embryo occurs.

The imprinted genes are marked as *deferentially methylated regions* (DMRs) and are frequently located at CpG islands in close proximity to gene enhancers. There are documented cases of serious diseases associated with malfunctioning imprinted genes. Over 100 imprinted human genes have been recognized to date. Imprinted genes are the major pathway for transgenerational epigenetics.[30]

B. Contrasts between methylation of vertebrate and invertebrate genomes

There are striking differences between the degree and pattern of genome methylation of invertebrate genomes compared with mammalian genomes. The divide probably occurs between vertebrates and invertebrates however since most vertebrates studied are mammals, with very few non-mammalian vertebrates included, this has not been clearly established. For a long time,

it was thought that methylation of invertebrates did not occur. For example, extensive studies of the nematode worm, *Caenorhabditis elgans,* revealed its genome lacked detectable methyltransferase. However recently isolated examples have been identified such as *Drosophila melanogaster* long thought to be free of CpG and DNA methyltransferase, has now been found to contain very low 5mC levels.

In general, the distribution pattern of methylated genes in invertebrates show large domains completely free of methylation with interspersed domains of relatively increased methylation, a pattern known as mosaic. "The variety of animal DNA methylation patterns highlights the possibility that different distributions reflect different functions for the DNA methylation system." [31]

There is also significant variability of methylation patterns over time and space. For example, during a discrete phase of early mouse embryonic development, methylation levels declined sharply to approximately 30% of the typical somatic level which is promptly restored during later embryonic development. Interspecies variations are also noted.[32]

C. Epigenetics and Identical, Monozygotic (MZ), Twins

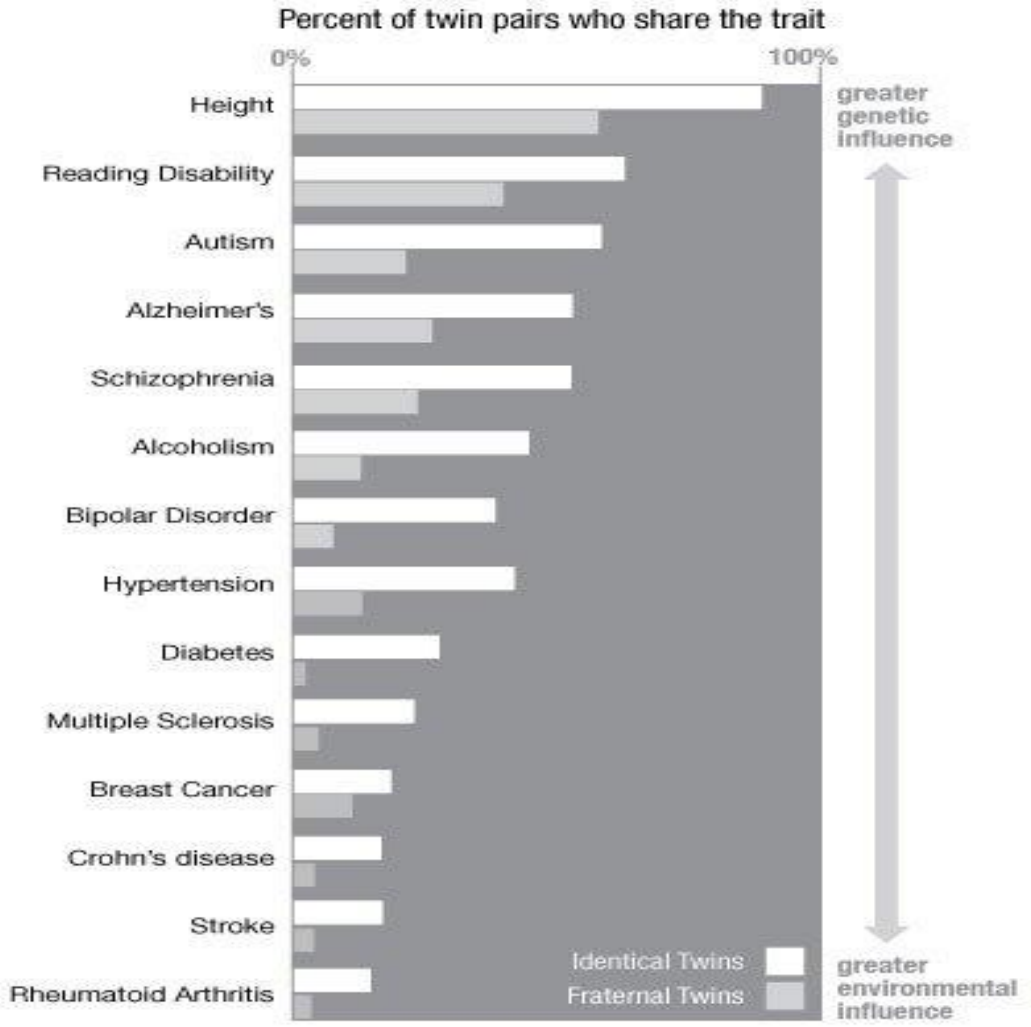
"Children conform to types, but no two are alike, even in the case of twins."[33]

Identical (MZ) twins present a fascinating demonstration of readily observable actions of epigenetics. MZ twins, as the term implies, share identical genomes, both babies having arisen from the same fertilized ovum, (zygote), hence monozygotic. Yet invariably they can almost always be recognized as different persons and the aging process always further accentuates individual differences.

Long-term studies of MZ twins in comparison with fraternal twins provide an ideal real-life laboratory for scientific investigation of the relative significance of "nature" versus "nurture." Comparing the incidence of specific diseases between MZ twins provides a measure of the degree that genetic versus environmental factors are causes. For example, if there is a high incidence of both twins contracting the same disease, careful investigation for genetic causes is indicated. On the other hand, if there is low concordance between both twins contracting the same disease, their different environmental factors should be carefully analyzed as likely causes. It is well established that with the passage of time, there is progressive divergence of their medical histories resulting from the accumulated effects of epigenetic and

other environmental factors. This phenomenon is known as “epigenetic drift.”

Below is a table[34] based on careful medical histories obtained from a large group of MZ twins and a cohort of fraternal twins. It is immediately apparent, as expected, that there would be a high concordance in the height of the MZ twins (at the top of the list) indicating that heredity is the major factor in determining a person’s height. The associated diseases listed in descending prevalence indicates that hereditary factors play a large role in a number of mental and psychosocial conditions, including, reading disability, autism, Alzheimer’s, schizophrenia, and bipolar disorder. A striking feature is the prominent role that heredity plays in the incidence of all of the listed conditions among the MZ twins when compared with the markedly decreased incidence among fraternal twins, again emphasizing the significance of genetics.



Comparing MZ and Fraternal Twins: A higher percentage of disease incidence in both MZ twins is the first indication of a genetic component. Percentages lower than 100% in MZ twins indicates that DNA alone does not determine susceptibility to the disease.[34]

In a study of 40 pairs of MZ twins, it was found that based on measurements of levels of DNA methylation (5mC) and histone acetylation, (AcH4 & AcH3) that 65% of pairs of twins had nearly identical epigenetic levels. The remaining 35% displayed significant differences in epigenetic profiles. The discordance in epigenetic profiles increased with age and was proportional to the amount of time the twins spent independently.

Extensive comparative epigenetic analysis was performed on three-year-old and 50-year-old MZ twins including a wide range of specific epigenetic molecular markers. These revealed a strikingly consistent parallel divergence with time, between the levels of methylation, acetylation, and other

molecular markers of epigenetic activity, which represent the individual epigenomes, consistent with the clinically observed phenotypic divergence. The scientifically determined molecular picture paralleled the phenotypic divergence observed, in time, between the 50-year-old AZ twins.[35]

D. Fertilization and DNA Fusion

As we discovered from studies of MZ twins, these hereditary factors will determine many physical traits such as sex, height, hair color (as well as when you will lose it), eye color, susceptibility to a number of diseases and the myriad of other physical features and traits that determine the child's physical and mental capabilities. These combined factors are known as one's genotype and are generally referred to as "nature." The other major determiner of who we are and who we will become is known as "nurture" and refers to all the environmental factors and experiences which control and direct the expression of our genes, such as when and where they are turned "on" or "off." These functions are controlled by the epigenome and the final results are known as one's phenotype.

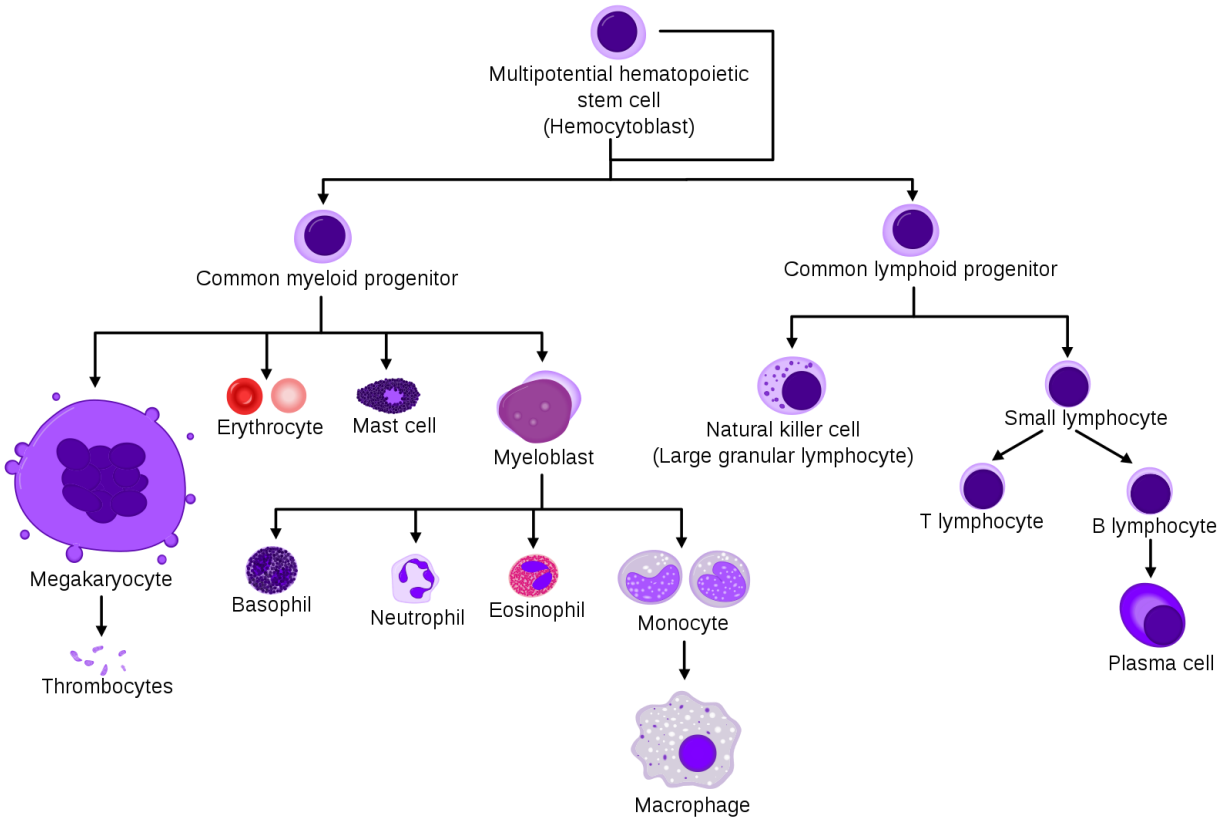
E. Stem Cells

Stem cells are usually classified in three major categories based on their potential to give rise to many different cell lines:

- Totipotent- can potentially become any cell throughout the entire body
- Multi potent- can become many different types of cells and cell lines
- Unipotent- a progenitor cell, capable of giving rise to a single cell line.

Every embryo starts with a single cell zygote, a totipotent stem cell, capable of differentiating into any of the hundreds of cell types in a multicellular organism. In humans it takes about a day for the first cell division to occur, it then takes about another day for the next cell division, becoming four cells, and by the fourth day, another division, becoming eight cells, and so on. Research on sheep embryos has confirmed that at the four-cell zygotic stage, each individual cell is totipotent, i.e. it can produce an entire sheep.

F. A multipotent hematopoietic stem cell.



Credit: A. Rad and Michael Haggstrom, M.D. CC-BY-SA 3.0 via Wikimedia commons.

Hematopoietic progenitor stem cells are multipotent cells capable of producing all of the circulating cells in the bloodstream. It can give rise to two first generation multipotent cell lines, the first a common myeloid progenitor and the second a common lymphoid progenitor. The common myeloid progenitor in turn gives rise to the megakaryocytes which produce platelets, erythrocytes or red blood cells, mast cells, myeloblasts which can then give rise to, basophils, neutrophils, eosinophils, and monocytes, which, in turn, can give rise to macrophages. The second multipotent progenitor, the common lymphoid progenitor gives rise to a natural killer cell or a large granular lymphocyte, and also small lymphocytes including T lymphocytes and B lymphocytes, which in turn give rise to plasma cells. Hematopoietic stem cells are frequently used for bone marrow transplants in the treatment of cancer such as leukemia as well as in autoimmune disorders.

There is an extremely rare severe immune system deficiency, caused by a genetic mutation, that is incompatible with life beyond a few months unless

recognized at birth and treated with a bone marrow transplant within the first 3 to 4 months of life that can ensure a normal life expectancy.

During embryo genic development, the selection of which of the multipotent stem cell genes are activated is largely an epigenetic function. The epigenome is extremely active during embryogenesis and early childhood. This is the period when there are many multi-potential stem cells requiring specific genetic signals specifying exactly which of hundreds of potential cell lines a given cell will become.

A fascinating experiment in which individual cells were transferred from one blastocyst stage mouse embryo to another, documented that the location of the cell can determine whether it will become a part of the embryo proper or will develop into extra-embryonic tissue such as placental or embryonic sac components. The position of the cell in relation to the inner cell mass (ICM) on the one hand or the trophectoderm on the other, appears to be the deciding factor, indicating spatial-location as an environmental epigenetic tractor.[36]

VII. Epigenetics and Childhood Development

On Wednesday, April 5, AD 30, Jesus, advised John Mark, who had become a serious youthful follower, "Your whole afterlife will be more happy and dependable because you spent your first eight years in a normal and well-regulated home. You possess a strong and well-knit character because you grew up in a home where love prevailed and wisdom reigned. Such a childhood training produces a type of loyalty which assures me that you will go through with the course you have begun."[37]

We will now address scientific information that strongly promotes child welfare based on recently expanded understanding of the importance of the epigenome during the formative period of childhood with emphasis on long term consequences, including a brief analysis of a report entitled "Working Paper no. 10," produced by the National Scientific Council on the Developing Child, located at Harvard University.[38] The biological life of the fetus begins with the fertilization of the ovum at which time the haploid genetic factors located in the ovum and sperm, become fused forming a zygote, reestablishing the full diploid compliment of DNA, that together will determine the new individual's genotype. It is well-established that epigenomes are functional during the intrauterine gestational period that are exacerbating to the nationwide epidemics of both type II diabetes[42,43] and obesity[39] which are metabolically intertwined. The personal life of the child

will begin at birth, at which time the environmental input will suddenly greatly expand and with it a concomitant increased potential for environmental mediated epigenetic action.[40,41]

A. Potential life-long benefits from positive epigenetic environment during childhood

"… [A] bad environment can very effectively spoil an excellent inheritance, at least during the younger years of life. Good social environment and proper education are indispensable soil and atmosphere for getting the most out of a good inheritance."[44]

Environmental epigenetic factors can be both positive and negative. Rich learning experiences can permanently affect brain function in a young child by associating learning with a pleasant and positive experience resulting in the child recognizing a lifelong learning experience as both pleasant and deeply satisfying.[45]

Just as positive experiences can result in beneficial lifetime changes in a person's mental attitude and outlook, negative experiences can also establish lifelong negative attitudes. Based on carefully established animal models, most commonly rats or mice, there is indirect scientific evidence to indicate that childhood abuse can have significant lifelong negative effects, which can be passed to subsequent generations.[46]

B. The Four Major Stages of Brain Development

- Neurogenesis
- Neuronal Migration
- Myelination
- Synaptogenesis

Brain growth and maturation is a complex process beginning early during fetal development as the organ systems of the body are being laid down. Brain development undergoes four major stages: neurogenesis, neuronal migration, myelination, and synaptogenesis. During neurogenesis the neurons and other supportive and structural cells appear. This is followed by neuronal migration in which neurons within the brain relocate and are rearranged. Myelination is the process of coating the nerve tracts with myelin, an insulating substance essential for nerve signal transmission. During synaptogenesis neural pathways are established and connections between the various individual neurons and brain components are matured. In most mammals these processes are largely complete at the time of birth, whereas in primates, it is much more protracted and in humans, extends to early puberty and beyond.[47]

C. Brain growth is a highly dynamic process.

Magnetic Resonance Imaging, MRI, has proven to be an ideal brain imaging procedure with no ionizing radiation, extremely high resolution, and high image contrast. Serial MRI brain scans, performed on children have demonstrated significant variation in rates of growth of different regions of the brain. For example, during early childhood, there is relatively rapid expansion of the gray matter shortly after birth which then begins to recede. Other areas of the brain also demonstrate variations in growth rates overtime.[48]

Scientific data establishes a functional relationship between neural stimuli and connectivity within the brain indicating a strong environmental influence on brain growth and function. The human brain is by far our most environmentally responsive organ as evidenced by individual creativity and the ability to react decisively to environmental threats and other conditions. No other organ has access to the extensive sensory input and the capacity to respond effectively as does the brain. Its ability to record experiences with long-term recall adds an additional dynamic epigenetic factor.[49]

In fact, multiple longitudinal studies of children exposed to severe conflict and other highly disturbing experiences, such as abusive situations, can acquire epigenetic changes that permanently alter the receptivity of the neural centers in the brain that control the level of the stress hormone cortisol. This is responsible for signaling the "fight or flight response" that in normal circumstances is an important protective and healthy autonomic response to potential danger. However, if there is continuous trauma such as exposure to frequent or regular violence, the brain receptors can become permanently modified, causing prolonged elevated levels of cortisol resulting in a pattern of recurrent overreaction to stress.[49]

Many epigenetic effects are time-sensitive and once established are very difficult, if not impossible, to reverse. The importance of a stable, safe, loving, caring home and community environment, saturated with quality adult – child interaction which serves to stimulate learning and creativity, cannot be overemphasized as a means to foster the positive potential of the epigenome during childhood.

D. How Early Experiences Alter Gene Expression and Shape Development

1. The central nervous plays a critical role throughout the entire childhood developmental process. It provides the vital link between the environment and the organism. The brain provides the link between all that is going on outside the body with what is going on inside. It is a two-way pathway on which environmental data is being gathered and appropriate reactions and adjustments are being formulated and directed. It is capable of assessing the effectiveness of its formulated responses. There is a significant element of trial and error, and reassessment and readjustments occur constantly. Normal brain development cannot occur without constant stimulation and activity. It is critical that this process is ongoing. It is essential for normal brain growth and development. Isolation and inactivity can be a paralyzing factor in brain growth and development.

There is a direct connection between developmental processes in the child's growing brain and his external environment. Included in these are environmental factors such as stress, abuse, nutrition, and toxins that have been shown to negatively impact the child's mental health and psychosocial development, with possible long-term consequences that can last a lifetime.

2. In addition to external signals, the neurons provide regulatory information, with the potential of directing the production of proteins within cells.

3. Gene regulatory proteins are involved in attracting or repelling enzymes that add or remove epigenetic markers.

4. Epigenetic markers control where and how much protein is made by a gene, effectively turning a gene on or off, thereby determining how brains and their bodies develop.

E. A functional epigenome is required throughout one's entire lifetime.

The chart below, borrowed from "Biology by the Numbers," reports the turnover rates of cell lines, many lasting for less than 10 days. The red blood cells are relatively durable, requiring replacement every 120 days. Since there are about 3×10^{13} red blood cells in the average human body, to keep abreast with replacement requirements, one must produce about 100 million new red blood cells every minute throughout one's adult lifetime.
We noted earlier that the epigenome is extremely active during embryological development because of the great number of new cell lines

being selected epigenetically. As this chart indicates, the work of the epigenome is not finished at adulthood, we need many replacement cells constantly.

cell type	turnover time	BNID
small intestine epithelium	2-4 days	107812, 109231
stomach	2-9 days	101940
blood Neutrophils	1-5 days	101940
white blood cells Eosinophils	2-5 days	109901, 109902
gastrointestinal colon crypt cells	3-4 days	107812
cervix	6 days	110321
lungs alveoli	8 days	101940
tongue taste buds (rat)	10 days	111427
platelets	10 days	111407,111408
bone osteoclasts	2 weeks	109906
intestine Paneth cells	20 days	107812
skin epidermis cells	10-30 days	109214, 109215
pancreas beta cells (rat)	20-50 days	109228
blood B cells (mouse)	4-7 weeks	107910
trachea	1-2 months	101940
hematopoietic stem cells	2 months	109232
sperm (male gametes)	2 months	110319, 110320
bone osteoblasts	3 months	109907
red blood cells	4 months	101706, 107875
liver hepatocyte cells	0.5-1 year	109233
fat cells	8 years	103455
cardiomyocytes	0.5-10% per year	107076, 107077, 107078
central nervous system	life time	101940
skeleton	10% per year	109908
lens cells	life time	109840
oocytes (female gametes)	life time	111451

Table 1: Cell renewal rates in different tissues of the human body. Values are rounded to one significant digit. Giving context through daily life replacement processes, we note that hair elongates at about 1 cm per month.[50]

Summary:

1. Epigenetics is among the most dynamic fields of molecular biology. In terms of the relative proportion of the human genome occupied by non-coding RNA genes which appear to be primarily concerned with epigenetic functions, compared with the portion of coding genes, one must conclude that the sum total of epigenetic activities, based on our present understanding, now surpasses the simple genetic functions addressed by the Central Dogma. Has the time for revision of the Central Dogma arrived?

2. The proportion of the total human genome devoted to protein synthesis is now dwarfed by the epigenetic portion devoted to the *control* of protein synthesis by the extensive epigenetic system of gene management.

3. Epigenetics plays a major role in the etiology, prognosis, and treatment of cancer. The recognition of the importance of CpG Island Methylator Phenotype (CIMP+) status in virtually all cancers is a major step forward in focusing cancer research on the molecular basis for all malignancies.

4. Epigenetics can exert a powerful control over genetics as illustrated by its near-complete inactivation of an entire chromosome, the X-chromosome in all female mammals, without which none would survive.

5. We are beginning to recognize the epigenetic potentials during child growth and development as documented by "Working Paper no. 10" authored by Jack P Shonkoff M.D., Chair, et.al., under the auspices of the National Scientific Council on the Developing Child, at Harvard University (2010). If the opening statement in their report is true, "New scientific research shows that environmental influences can actually affect whether and how genes are expressed. Thus, the old idea that genes are 'set in stone' or that they alone determine development have been disproven." If this is true, and I am personally convinced it is, by extrapolation it is applicable not only to children but to humans of all ages. And when one factors in the trans-generational potential of epigenetics, the impact on societal improvement is unlimited.

6. In our study of science, as our powers of observation expand as a result of technological advances and engineering capabilities in the construction of machines capable of extending our vision to the far reaches of the universe, and at the same time reaching down to the molecular level of the inner workings of the abundant surrounding life of which we are part, we inevitably encounter phenomena that does not fit with a theory of causation based entirely on mechanistic probability.

We will begin with simple dilemmas such as what caused the non-random distribution of CpG islands throughout mammalian genomes? What is the explanation of the puzzling inconsistencies exhibited by the methyltransferase activities?

What is the origin of the design and structure of the DNA molecule that is phenomenal in so many ways of which Francis Crick was keenly aware? Similarly, how were the design and the instructions derived for the thousands of complex proteins, exemplified by RNA polymerase II, that performs its copying of DNA onto RNA at incredible speed, essentially flawlessly, providing the information to assemble amino acids for the thousands of proteins in each living cell? How could the concept of an information molecule be result from an entirely mechanistic molecular process? How was the Universal Genetic Code conceived? How did the Universal Genetic Code originate at the onset of the evolutionary cycle, when its very existence is generally conceived by mechanistic Darwinists to have been derived from the very evolutionary process that we have recently learned it actually directs?

Finally, we should not ignore the nanomachines that are scurrying about in every cell in our bodies performing minute essential mechanical activities that in many ways are reflective of the genetic and epigenetic processes here under consideration. What form of supervision could explain their extremely efficient and apparently cooperative manner of functioning?

Acknowledgements: I want to express my deepest gratitude to my son, Michael, for his extensive technical advice and assistance, and to Betty, my wife of 62 years, who, as always, gave her support and served as a reliable sounding board during this project.

End Notes

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