Epigenetics

Grade: First year – Ashur Medical college
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Module: HDTD

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Objectives



- Definitions Epigenetics.
- Find out the interlink between Genetics and Epigenetics.
- Identify histone protein structure.
- Identify DNA methylation ,histone protein modifications and
- other epigenetic modifications.

Describe the **Factors Affects Epigenetics.**

Describe some examples in Epigenetics.

Question ??



- What makes phenotypic difference in genetically identical cells (or organisms) express their genomes differently??
- Epigenetics describes phenomena in which genetically identical (organisms) express their genomes differently, causing phenotypic difference.

- What makes genetically identical cells differentiate to specific type of celles e.g. neurons ,muscle cells , liver cells ,etc.? Or becomes a malignant cell?
- Epigenetic modifications can manifest as commonly as the way cells terminally differentiate to end up as skin cells, liver cells, brain cells, or develop malignant cells.

Epigenetics



Epigenetics is the study of changes in organisms caused by modification of gene expression that not change the DNA sequence .

Key words in Epigenetics

- Nucleosome: DNA+ Histone
- Chromatin : repeated units of nucleosomes.
- **Epigenomic** modifications : Modifications (changes) in DNA or its histone epigenome or noncoding proteins.
- Modifications marks the DNA or gene (labels with sign OR trait).
- Modifications :DNA methylation & Histone modifications and noncoding RNA modifications.
- Histone tail (N-terminus) stick out (to go past the surface or edge). Its residues are subjected to modifications.
- Turn genes "on" : loosely wounded DNA around histone proteins , active gen, unwrapped genes , easily accessible genes transcription activation .
- Turn genes "off": unreadable gen - silenced :tightly wounded (wrapped) around histone , transcription repression.
- Epigenetic tags: epigenetic modifications or marks, are chemical modifications to DNA and histone proteins (chemicals tags)
- Tages and marks (labels) in epigenetic memory profile labelled in genome (heritable epigenomes) (all past events). E.g Methyl and acetyl tags.
- .



Epigenetics : facts[1]



- A chemical modifications change DNA function by turn genes "on" or "off" controlling which proteins are produced in particular cell.
- These modifications do not change the DNA sequence or genome.
- By modifications (changes), epigenome have various gen expressions according to cell types , disease states, and in response to different stimuli.

Epigenetics facts [2]



- The epigenome is made up of chemical compounds attach to (DNA and DNA proteins) that direct actions which alter gene expression.
- An epigenome consists of an existing record of the chemical changes to the DNA and histone proteins of an organism; these changes can be heritable (via meiosis and mitosis).. Changes to the epigenome can result in changes to the structure of chromatin (DNAs & proteins) and changes to the function of the genome by turning genes (on) or (off) controlling the production of proteins in a particular cell.
- The modifications occur as a natural process of development and tissue differentiation and can be altered in response to environmental exposures or disease.

Epigenetics facts [3]



- ✓When epigenomic compounds attach to DNA and modify its function, they are said to have "marked" (labeled) the genome (with trait). These marks do not change the sequence of the DNA. Rather, they change the way cells use the DNA's instructions.
- ✓The marks are sometimes passed on from cell to cell as cells divide. They also can be passed down from one generation to the next.

post transcription modifications

Mechanisms of Epigenetics: Epigenetic tags (marks)

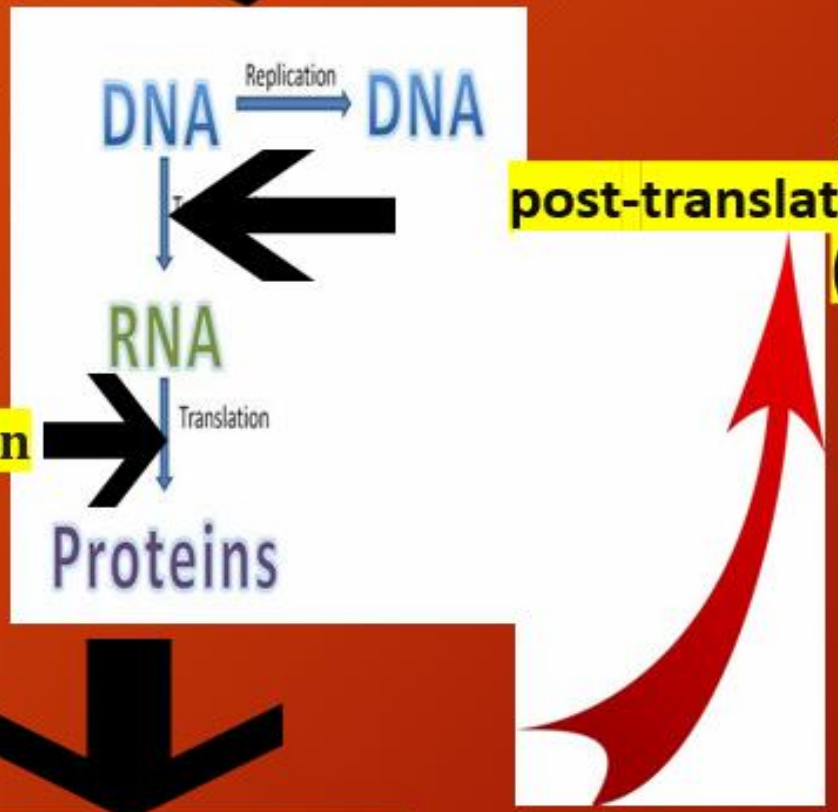


- Epigenetic changes regulate gene expression by acting as gatekeepers, blocking or allowing access to a gene's 'on' or "off" switch. Chemical tags (such as methyl) are added directly to DNA or onto histones.
- Other chemical tages like acetylation etc are added to histones but not to DNA.

In general, epigenetic changes are brought about by1- DNA methylation 2- histone modification 3- post transcription RNA modifications .

Epigenetic modifications

A- DNA methylation



B-Histone modification
post-translational modifications
(PTMs)

C-Post-transcriptional mRNA modification

B-Histone modification
post-translational modifications
(PTMs)

1- DNA methylenation



Addition of a methyl group (CH3) to the Cytosine (C) nucleobase in a DNA sequence to the 5' carbon atom in the pyrimidine ring forms 5-methylcytosine.

It occurs predominantly in the context of CpG dinucleotides, where a cytosine is followed by a guanine in the DNA sequence.

The "p" in CpG indicates a phosphodiester bond that connects the cytosine and guanine.

Enzyme :The methyl modifications (tags) catalyzed by DNA methyltransferases) , where it:

-Blocks the proteins that attach to DNA to "read" the gene.

Inhibit the binding of transcription factors.

- Reduces gene expression(Turn genes off) leading to transcriptional silencing .

- **This methyl groups can be removed by demethylation which turns genes "on."**



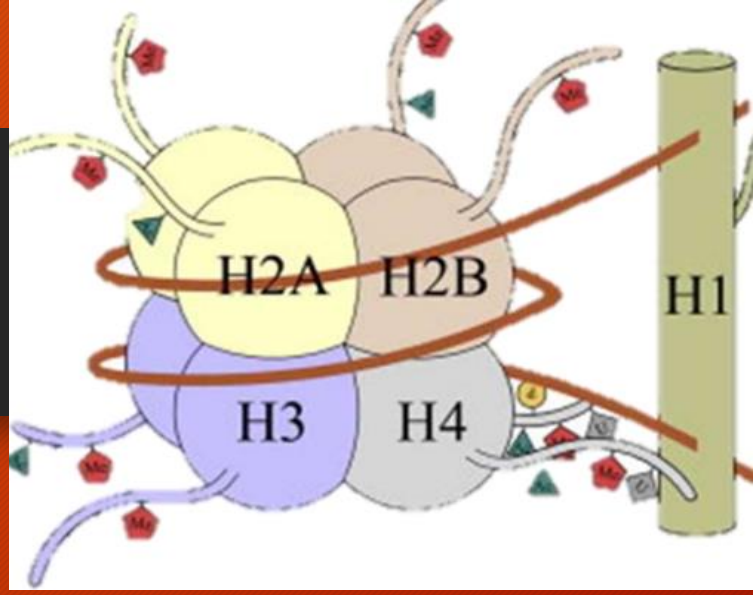
- Azacitidine is a chemical analogue of the RNA nucleoside cytidine.
- It inhibites DNA methyltransferase, causing hypomethylation of DNA and at high doses.
- Azacitidine is used for the treatment of certain leukemias.

Cytosine (C)	cytidine





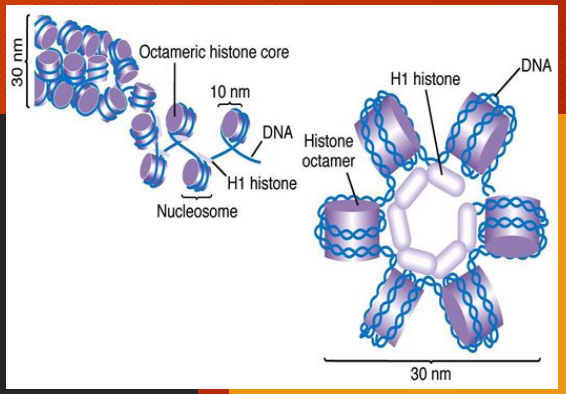
2- Histone modification



- Introduction

Nucleosome: DNA+ Histone
Chromatin : repeated units of nucleosomes.

- **Each nucleosome DNA is wrapped (tightly wound) around a set of eight proteins called histones (histone octamer).**
- **Each histone octamer is composed of two copies each of H2A, H2B, H3, and H4 histones .**
- **Histone proteins have tails (N-terminus)that stick out (to go past the surface or edge). These tails have (chemical residues) are covered with epigenetic tags (chemical residues) that affect the way the protein reacts with DNA.**



Histone tails are subject to a variety of modifications at various residues (places). These modifications take place in the positively charged tails of the histone proteins, which interact with the DNA and affect chromatin structure, transcription of genes ,gene regulation and DNA damage and repair.

Chemical groups can be added or removed from histones to make the histones more tightly or loosely packed, turning genes "off" or "on."



Histone **Post-translational** modification

PTMs usually are seen in the proteins with important structures/functions such as secretory proteins, membrane proteins and histones

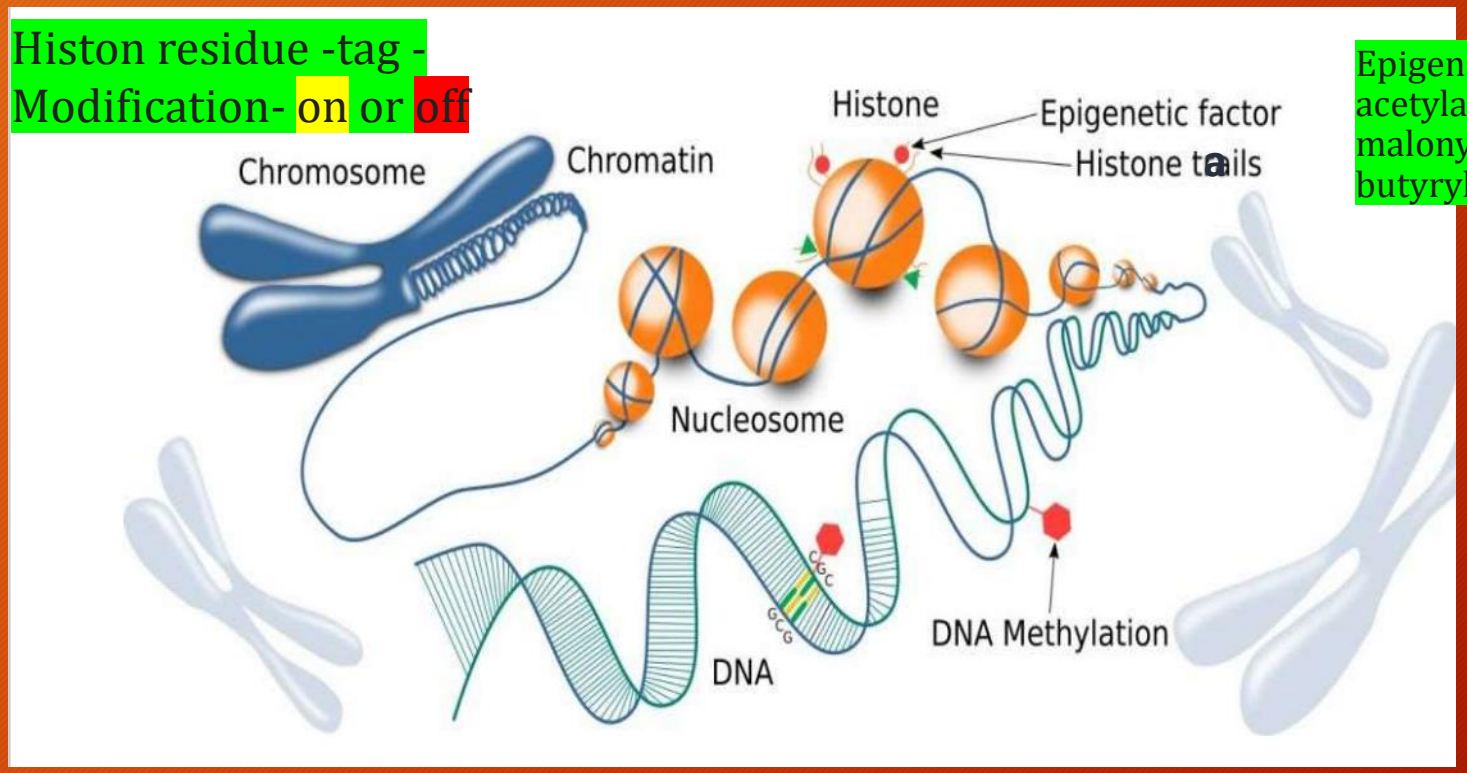
Histone modification refers to chemical alterations of histone proteins, which are involved in packaging DNA into chromatin and regulating gene expression.
The mechanisms of histone modification involve enzymes that add or remove chemical groups, such as acetyl, methyl, or phosphate groups, to specific amino acids (residues) on the n-terminus(histone tails).
These modifications can affect chromatin structure and the accessibility of DNA to transcription factors and other regulatory proteins, thereby influencing gene expression.
Each modification can have different effects on gene expression, depending on the specific histone residue modified and the context in which it occurs"

chemical groups +amino acids (residues) = Histone modification



- Modifications to histones can loosen or tighten the DNA reel, altering which genes are exposed.
- Having tightly wrapped genes =unreadable , silenced or inactive genes (turned off).
- Unwrapped genes are easily accessible (turned on genes).
- Modifications can occur at different amino acids on different histones (two each of H2A, H2B, H3, and H4) and create many changes in the histone. E.g. the amino acid Lysine residue attach to acetyl tags in acetylation.

Histon residue -tag -
Modification- on or off



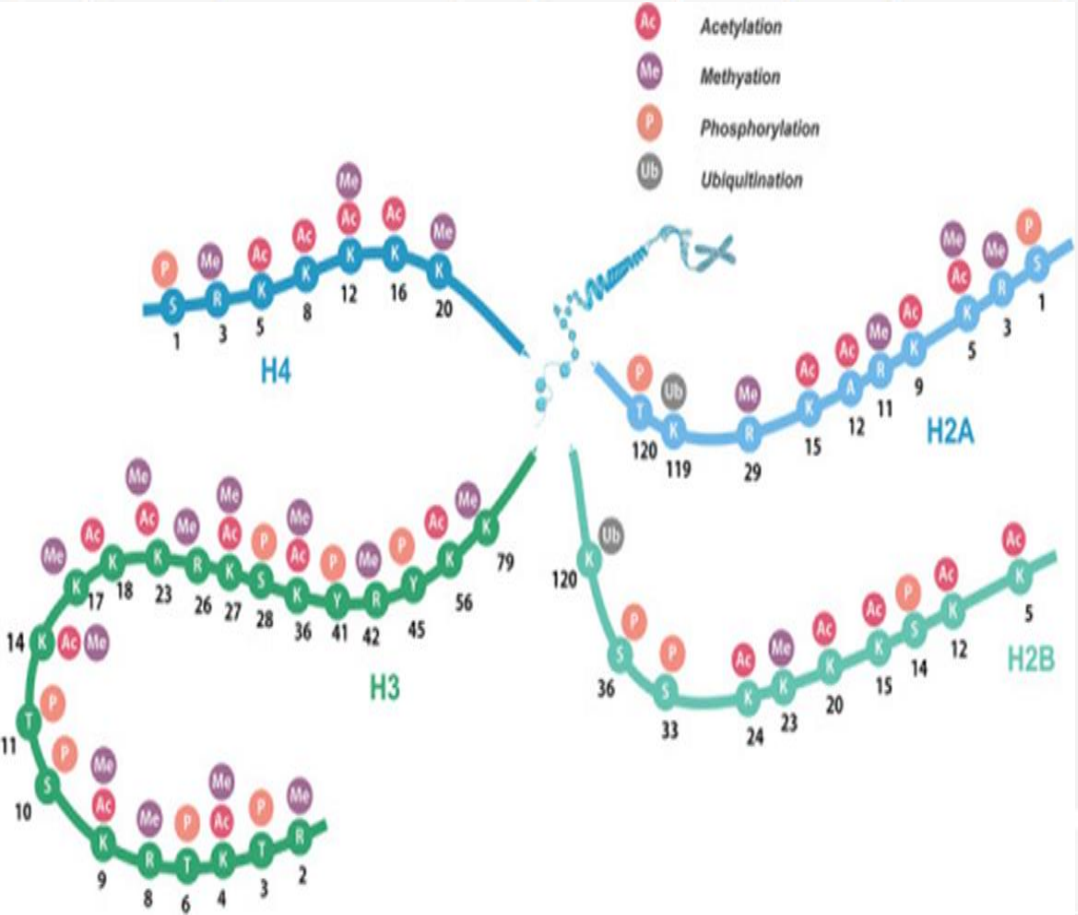
Epigenetic factor e.g. histone methylation, acetylation ,phosphorylation, ubiquitination, malonylation, crotonylation, propionylation, butyrylation, and so forth.

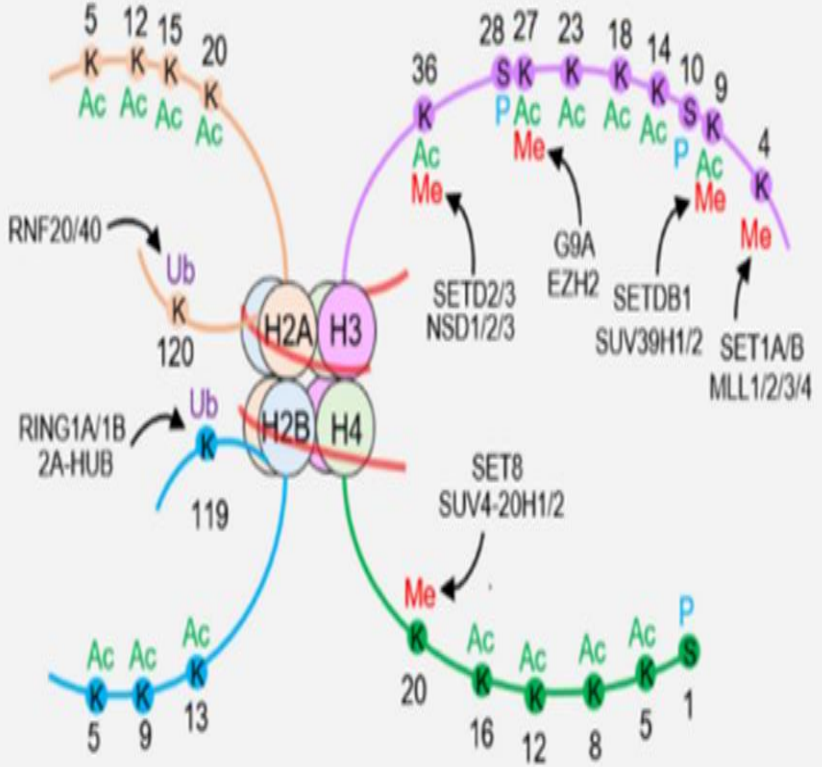
Histone	residues	Modification	examples
Histone H2A	Lysine	acetylation ,methylation , ubiquitination ADP-Ribosylation (H2A-ADPr) Phosphorylation Variant Histones (e.g., H2A.X)	(H2Aac), (H2AK5me, H2AK9me, H2AK13me) (H2AK119ub) (H2AS1ph)
Histone H2B	lysine	acetylation , methylation ubiquitination Phosphorylation Crotonylation	(H2BK5ac, H2BK12ac) (H2BK4me, H2BK20me) (H2BK120ub) (H2BS14ph) (H2BK120cr)
Histone H3	lysine , arginine, serine	acetylation, methylation, phosphorylation, and ubiquitination	lysine residues acetylation's:H3K9ac, H3K14ac, H3K18ac, H3K23ac, H3K27ac, H3K56ac. Arginine methylation:(H3R17me), (H3R2me)
Histone H4	Lysine serine	acetylation, methylation, ubiquitination, and phosphorylation	Lysine 5 (K5): acetylation (H4K5ac), methylation (H4K5me), and ubiquitination (H4K5ub). Lysine 8 (K8): can be acetylated H4K8ac, methylated (H4K8me), , or ubiquitinated (H4K8ub).. Lysine 12 (K12): is subject to acetylation (H4K8ac), and methylation (H8K5me). Lysine 16 (K16): can be acetylated H4K16ac. Serine 1 (S1):histone H4 Phosphorylation at serine 1 (S1), serine 2 (S2), or serine 47 (S47) Phosphorylation.



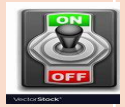


Schematic diagram of histone modification landscape. The nucleosome consists of one H3-H4 tetramer, two H2A-H2B dimers, and the surrounding DNA. There are many modifications on the histone tail, including histone methylation (Me), acetylation (Ac), ubiquitination (Ub), and phosphorylation (P).

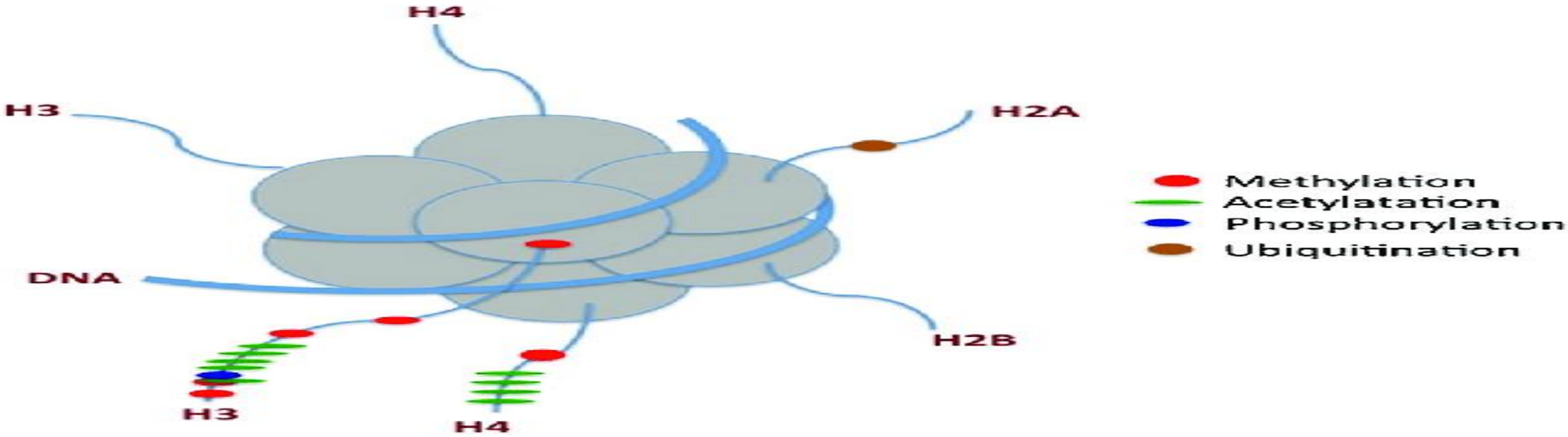






Histone modifications	Residue	enzyme	Action in general	Examples :Histone type &residue no. Action
Methylation (+CH3)	lysine or arginine 	DNA methyltransferases (DNMTs)	Transcriptional activation or repression.	4 (H3K4) and Lysine 36 (H3K36), Lysine 4) Lysine 9 (H3K9) and Lysine 27 (H3K27) Activation , Repression
Acetylation (+COCH3)	lysine 	Histone acetyltransferases (HATs)	Generally activation of Transcription. S.T. suppression	H3+H4 Compete with H3K9 (H3K9me) s.t H4K16 repression
Deacetylation	lysine	histone deacetylases (HDACs)	Suppression of Transcription	
Phosphorylation	serine, threonine, or tyrosine 	Kinases +po4 Phosphatases -po4	Transcriptional activation or repression.	H3 may promote chromatin condensation during mitosis. Cellular Communication then initiate intracellular signaling cascade ,etc
Ubiquitination	lysine 	E3 ligases + ubiquitin deubiquitinases (DUBs) - ubiquitin	transcriptional activation or repression.	H2B K120ub :DNA Repair signal transduction etc. H2Ak119un Role in spermatogenesis, meiosis,
Sumoylation(addition of small ubiquitin-like modifier (SUMO)	lysine 	SUMO ligases +SUMO, SUMO proteases-SUMO	Generally transcriptional repression.	E.g. DNA Repair Positive or negative impact on DNA Repair
ADP-ribosylation	lysine 	Poly(ADP-ribose) Polymerases	Generally DNA repair etc. context-dependent	H2B, particularly at serine 6 (H2B S6)
Citrullination 	Deamination Converts arginine residues to citrulline	Peptidyl Arginine Deiminases	Generally Activation of Gene Expression	rheumatoid arthritis: Activation of Immune Response. (H3R2) (H3R8)

Butyrylation and Crotonylation , Propionylation , O-GlcNAcylation , Proline Isomerization, Histone H2A Variants, Multipartite Modifications.



- **Post-translational modifications:**
  - **Acetylation** – Lys
  - **Methylation** – Lys and Arg
  - **Phosphorylation** – Ser and Thr Also tyrosine
  - **Ubiquitination** – Lys

2.1-Histone Methylation

Methylation (+CH3)	lysine or arginine	DNA methyltransferases (DNMTs)	Transcriptional activation or repression.	4 (H3K4) and Lysine 36 (H3K36), Lysine 4) Lysine 9 (H3K9) and Lysine 27 (H3K27) Activation , Repression

Depending on the specific residue and degree of methylation, it can be associated with either transcriptional activation or repression.

Enzyme :histones methyl transferase (HMTs). Both arginine and lysine residues can be methylated. Methylation impacts how other proteins, such as transcription factors, interact with nucleosomes.

- Histone methylation does not alter the charge of the histone, but it alters the chromatin structure.

Examples

Methylation of lysine can lead to either gene activation or repression, depending on the specific lysine r e of methylation.4 (H3K4) and Lysine 36 (H3K36), Lysine 4)



- Lysine 9 (H3K9) and Lysine 27 (H3K27)
- Activation , Repression

2.2. Histone Acetylation

Acetylation (+COCH3)	lysine	Histone acetyltransferases (HATs)	Generally activation of Transcription. S.T. suppression	H3+H4 Compete with H3K9 (H3K9me) s.t H4K16 repression
Deacetylation	lysine	histone deacetylases (HDACs)	Suppression of Transcription	

Generally associated with transcriptional activation as it neutralizes the positive charge on lysine residues.

Turn genes "on" : loosely wounded DNA around histone proteins , active gen, unwrapped genes , easily accessible genes = gene activation.

Enzyme: histone acetyltransferases (HATs).

- HATs transfer the acetyl group of CoA and acetylCoA to specific lysine residues at the histone N-terminus, particularly in H3+H4 .

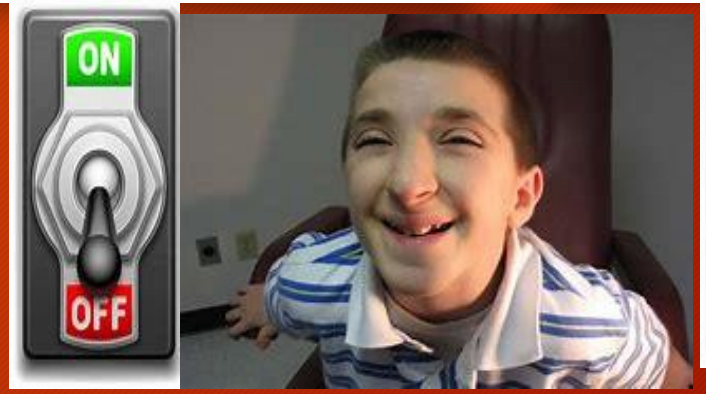
E.g. H3K9ac compete with (H3K9me)



Histone Deacetylation :

Deacetylation	lysine	histone deacetylases (HDACs)	Suppression of Transcription

- Increases interaction of DNA and histones.
- Represses transcription (usually) .

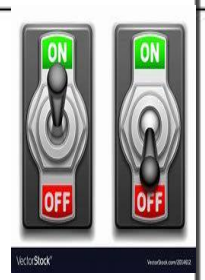


The Rubinstein-Taybi syndrome (RSTS) is a developmental disorder with variable clinical heterogeneity characterized by a typical facial appeance , distal limb abnormalities, and mental retardation .Its physiopathology is based primarily on an epigenetic mechanism. Studies have shown that neuronal histone acetylation mainly involving H2B and H2A is reduced in RSTS.

This deficit was rescued by treatment with an inhibitor of histone deacetylases (HDACi).



Difference between Histone Methylation and Acetylation

	Methylation	Acetylation
Modification Site	Lysine and Arginine	Lysine
Stability	Generally reversible	Generally stable
Function	Transcriptional Activation OR Repression 	Generally Transcriptional Activation 

2.3.Phosphorylation:



— Phosphorylation — Ser and Thr s.t tyrosine

Histone phosphorylation has a dual role in gene regulation, contributing to both activation and suppression of gene expression.

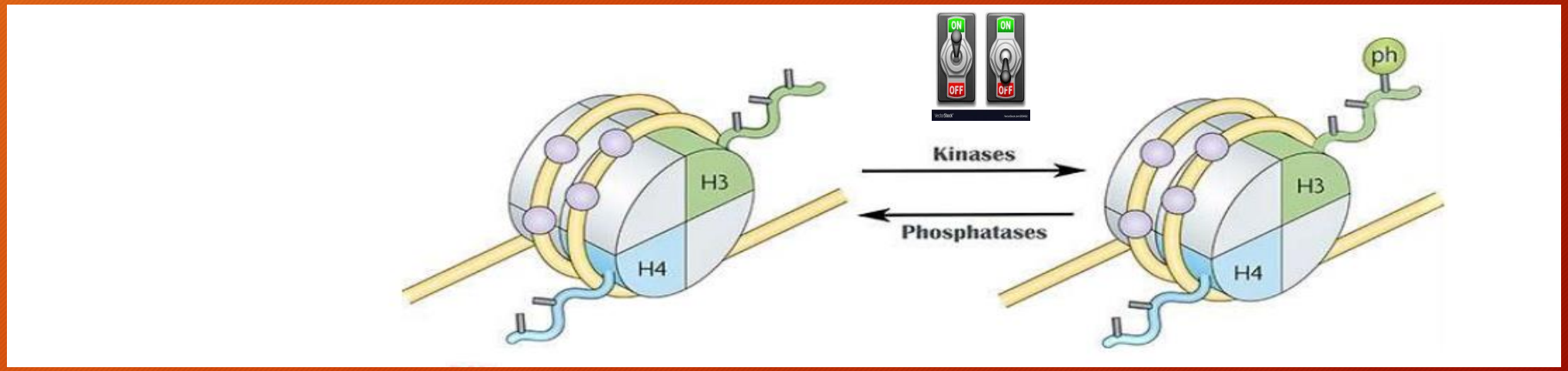
Histone phosphorylation mostly occurs on serine (S) and threonine (T) residues, but also occurs on tyrosine (Y) residues.

Enzymes: specific protein kinases (PKs), whereas protein phosphatases (PPs)mediate removal of the phosphate group.

Histone phosphorylation of the N-terminus plays a direct role in mitosis, cell death, DNA damage repair, DNA replication , DNA recombination and Cellular Communication and initiation of intracellular signaling cascade ,etc

Phosphorylation	serine, threonine, or tyrosine	Kinases +po4 Phosphatases -po4	Transcriptional activation or repression.	H3 may promote chromatin condensation during mitosis. Cellular Communication then initiate intracellular signaling cascade ,etc

During mitosis, H3 histones undergo phosphorylation at serine 10 (S10) and serine 28 (S28) residues. This phosphorylation is carried out by kinases. The phosphorylation of histone H3 is associated with the formation of condensed and highly visible chromosomes. It is a reversible process, and dephosphorylation of H3 histones occurs during the subsequent stages of the cell cycle.



2.4. Ubiquitination



Ubiquitination	lysine	E3 ligases + ubiquitin deubiquitinases (DUBs) -ubiquitin	transcriptional activation or repression.	H2B K120ub :DNA Repair ,signal transduction etc. H2Ak119un:

- Small protein molecules called ubiquitins are covalently attached to target proteins.
- Can lead to both activation and repression of gene transcription, depending on the specific lysine residue modified.
- Functions :DNA repair ensuring genomic integrity and signal transduction.
- Examples :
- H2B K120ub :DNA Repair etc.

H2Ak119un: Plays role in spermatogenesis and miosis.

2.5.Sumoylation



Sumoylation(addition of small ubiquitin-like modifier (SUMO)	lysine	SUMO ligases +SUMO, SUMO proteases-SUMO	Generally transcriptional repression.	E.g. DNA Repair Positive or negative impact on DNA Repair

Small ubiquitin-like modifier (SUMO) proteins (100 amino acids in length) can be attached to lysine residues. Sumoylation regulates chromatin structure and gene expression such modification influences chromatin organization and transcriptional regulation.

ADP-ribosylation	lysine	Poly(ADP-ribose) Polymerases	General DNA repair etc.	H2B, particularly at serine 6 (H2B S6)

ADP-ribosyl groups are added to lysine residues. This modification influences DNA repair and chromatin remodeling.

2.6. Citrullination:

Citrullination	Deamination Converts arginine residues to citrulline	Peptidyl Arginine Deiminases	Generally Activation of Gene Expression	rheumatoid arthritis: Activation of Immune Response. (H3R2) (H3R8)

Deimination (or Citrullination): Conversion of arginine residues to citrulline through the removal of the amino group. can affect chromatin structure and is implicated in various diseases.

This modification involved in gene regulation and immune responses.

2.7. Others

Butyrylation and Crotonylation , Propionylation , O-GlcNAcylation , Proline Isomerization, Histone H2A Variants, Multipartite Modifications.

3- **Post RNA transcription modification of** (Non-coding RNA molecules).

Post-transcriptional mRNA regulation refers to the processes that occur after messenger RNA (mRNA) has been transcribed from DNA but before it is translated into a protein.

- **DNA instructions are used for making coding and non-coding RNA.**
- **Small RNA molecules can regulate gene expression by binding to specific mRNA sequences.**
- **Coding RNA is used to make proteins.**
- **Non-coding RNA helps control gene expression by attaching to coding RNA, along with certain proteins, to break down the coding RNA so that it cannot be used to make proteins.**
- **Non-coding RNA may recruit proteins to modify histones to turn genes "on" or "off."**

- Examples:

3.1.Transfer RNA (tRNA) Modifications.

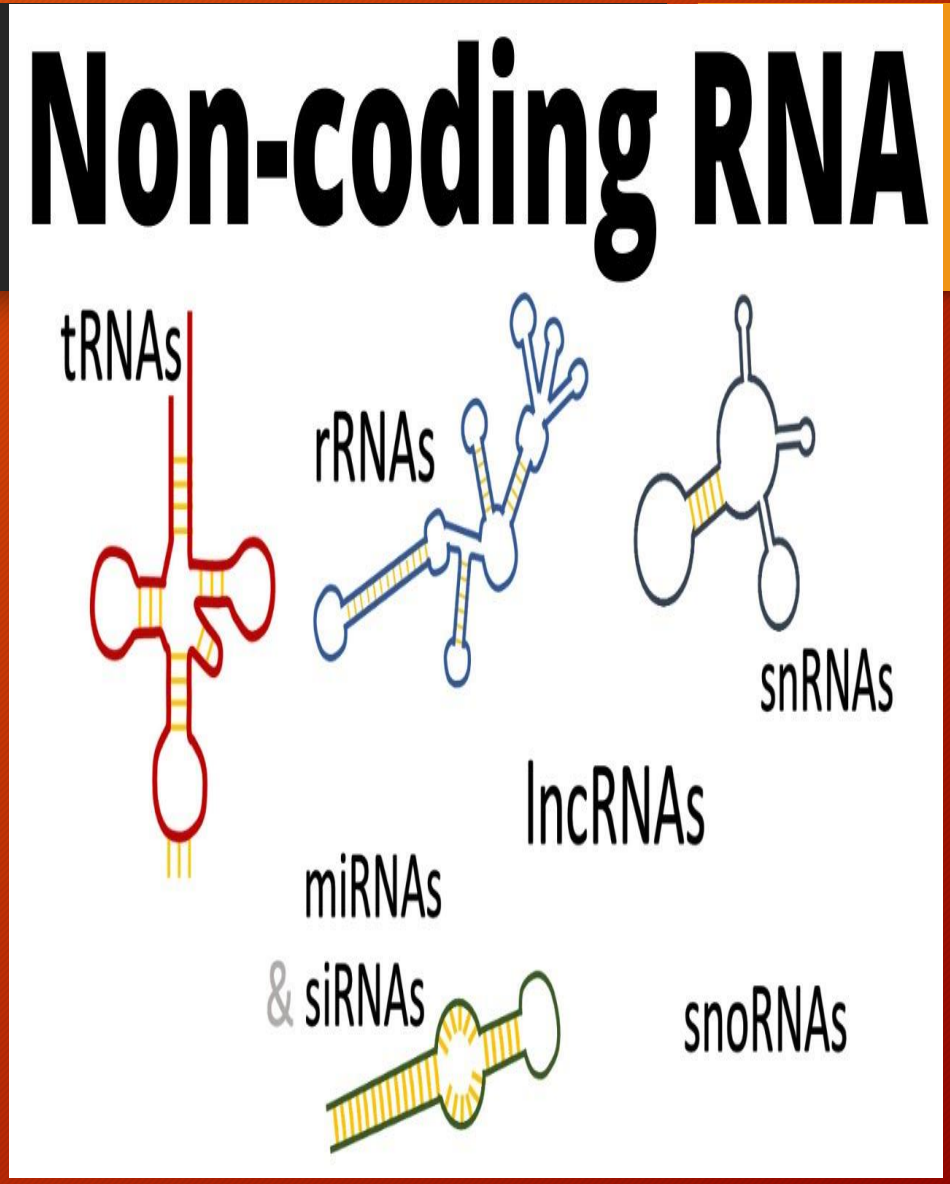
3.2.Ribosomal RNA (rRNA) Modifications.

3.3.Small Nuclear RNA (snRNA) Modifications.

4.4. MicroRNA (miRNA) Modifications.

4.5. Long Non-coding RNA (lncRNA) Modifications.

4.6. Small nucleolar RNAs (snoRNAs)Modifications.



Epigenetic Inheritance:

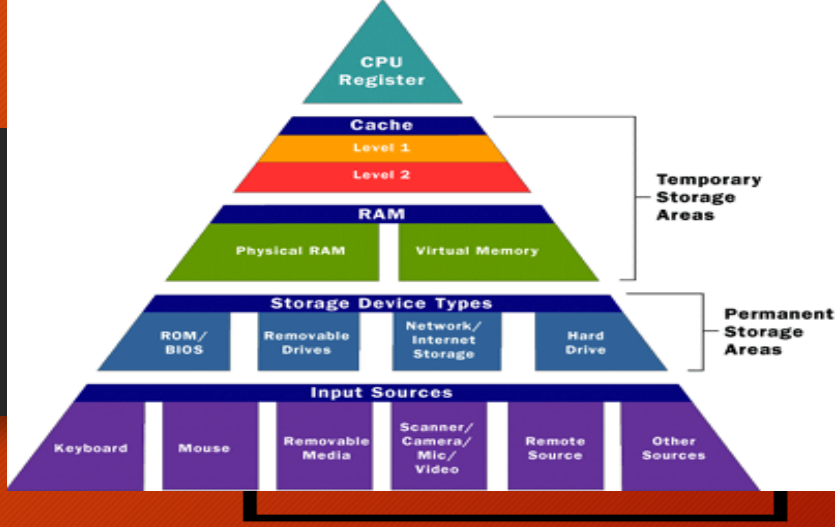
- ✓ **An epigenome consists of an existing record of the chemical changes** (marks) **to the DNA and histone proteins of an organism; these changes can be heritable (via meiosis and mitosis) and** sometimes passed on from cell to cell as cells divide. I.e. Parents experiences that affect genes can be passed to future generations in the form of epigenetic tags.

Epigenetic changes can accumulate throughout a lifetime.

Heritable changes in gene expression cause change in phenotype without a change in genotype.

Imprinted tags are genes that still contain the epigenetic tags from the sperm and egg.

Some genes retain their epigenetic tags even after fertilization. These imprinted genes can be passed down from one generation to the next.



- **Epigenetic Cell Memory ensures cells remain specialized throughout an organism's lifetime.**
- **A cell must first "know" that it is an eye cell before it can decide whether to become part of the lens or the cornea.**
- **The epigenome allows cells to remember their past experiences long after the signals fade away.**
- **The epigenetic memory of a cell defines the set of modifications to the (DNA) that do not alter the DNA sequence and have been inherited from the cell from which it descends. Such modifications can alter gene expression and therefore the properties and behavior of the cell.**

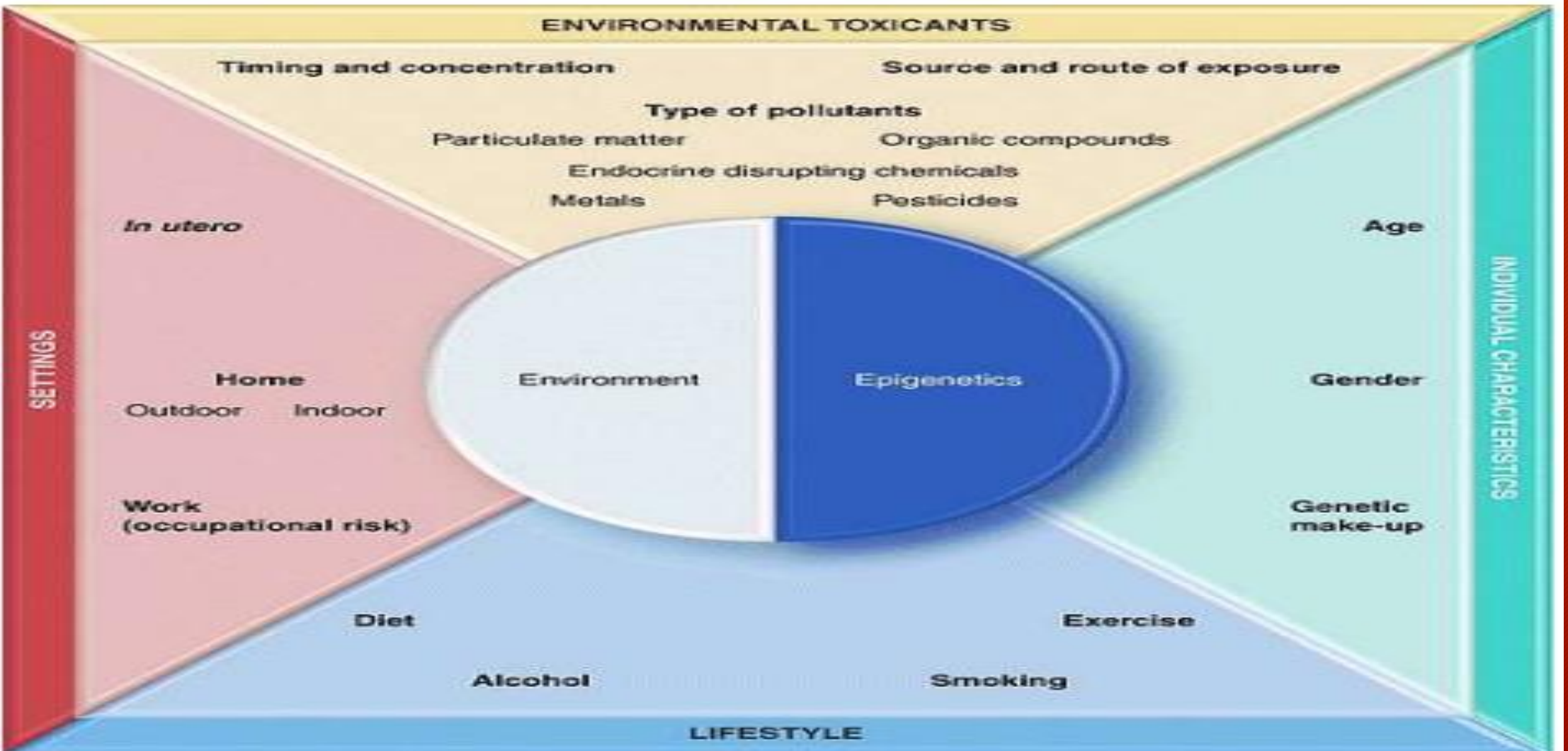
- **Epigenetic memory is an ability of the cells to stably retain and transmit the unique gene expression patterns to the daughter cells.**
- **It is encoded by the epigenetic marks (tags) and the associated epigenetic memory factors. Epigenetic tags give the cell a way to "remember" long-term what its genes should be doing.**
- **The epigenomic code for each gene could be unique to specific cell type or disease condition and therefore the same genome can acquire different collections of epigenomic codes to form the characteristic epigenome, which defines the overall cellular properties.**

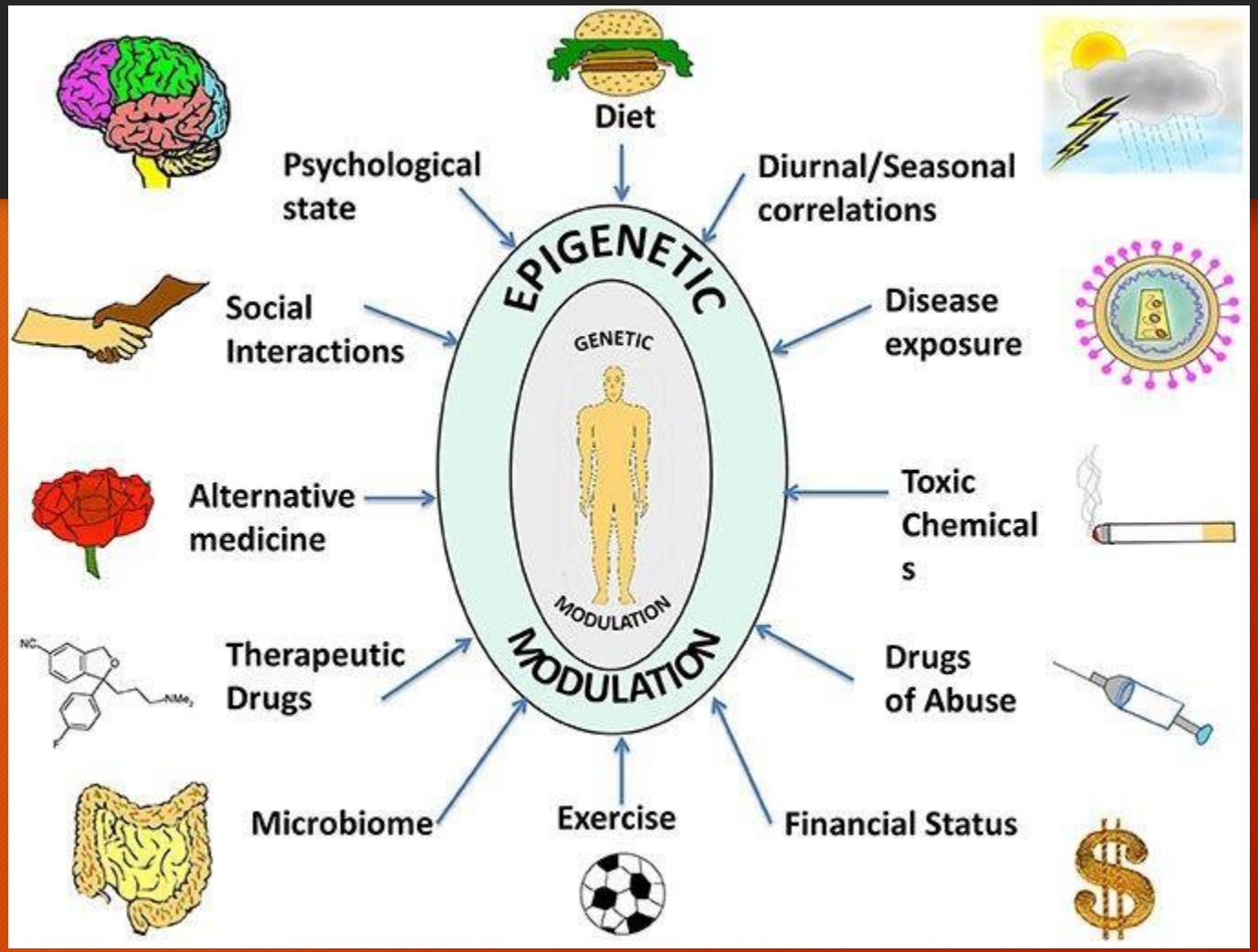
In a differentiated cell, only 10 to 20% of the genes are active. Different sets of active genes make a skin cell different from a brain cell.

Epigenetics and Reversibility

Not all epigenetic changes are permanent. Some epigenetic changes can be added or removed in response to changes in behavior or environment. .

What factors affect gene expression?




Diet
Psychological state
Diurnal/Seasonal correlations
EPIGENETIC
GENETIC
MODULATION
MODULATION
Social Interactions
Disease exposure
Alternative medicine
Toxic Chemicals
Therapeutic Drugs
Drugs of Abuse
Microbiome
Exercise
Financial Status

Examples of Epigenetics Phenomena

1- Identical twins and epigenetics :

Identical twins begin life with similar epigenomes, may develop differently depending on their lifestyle.

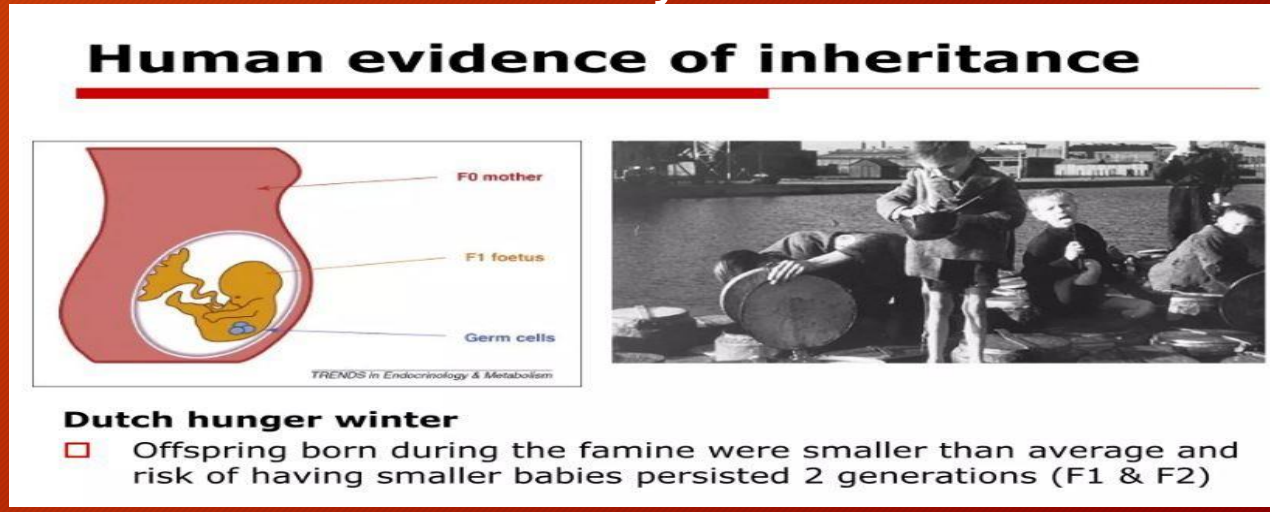
2-Epigenetic in Cancer.

3- sleep deprivation has been linked to alterations in DNA methylation

4-Fetal Alcohol Syndrome- methylation.

5-Epigenetic Effects of Trauma and Stress .

6-The Barker Hypothesis



- *7- Mycobacterium tuberculosis* causes tuberculosis. Infections with these germs can cause changes to histones in some of immune cells that result in turning "off" the *IL-12B* gene which weakens the immune system and improves the survival of *Mycobacterium tuberculosis.*
- 8-Several studies suggest that epigenetic modifications, like DNA methylation and histone modifications, are associated with ASD.
- 9- Epigenetics and Addiction.

10-Influence of Socioeconomic Status.

11-Epigenetics and Immunity.

12-Epigenetic Effects of Prenatal Care

Integration

- Pathogeneses of diseases DNA Structure and genetics.
- Hypomethylation (Pharmacology).
- Central Dogma ,Nucleotides and DNA.




THANK
YOU