Epigenetics:

THE STUDY OF THE INHERITABLE

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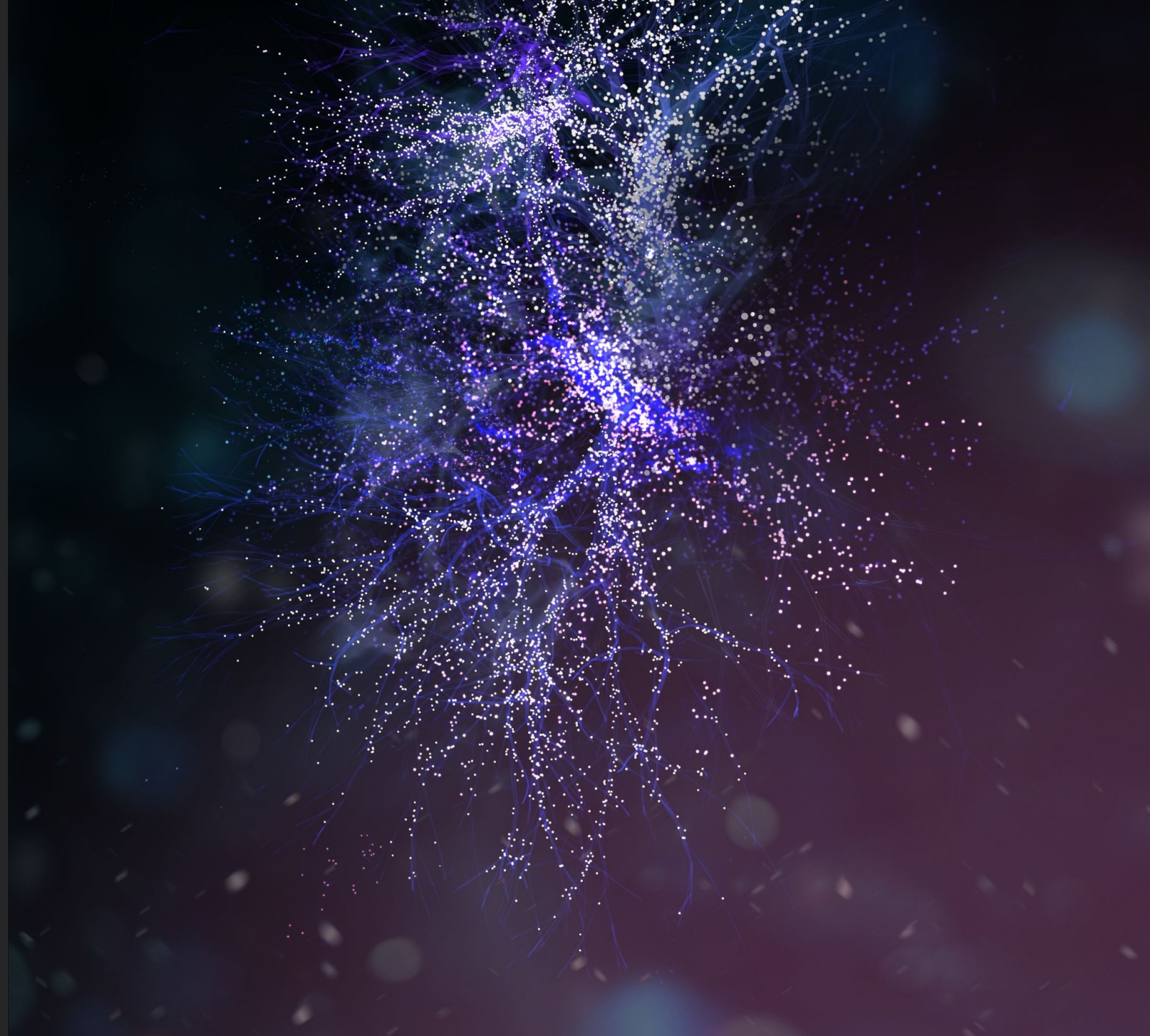


Definition:

Study of the **HERITABLE** phenotype.

Quiz

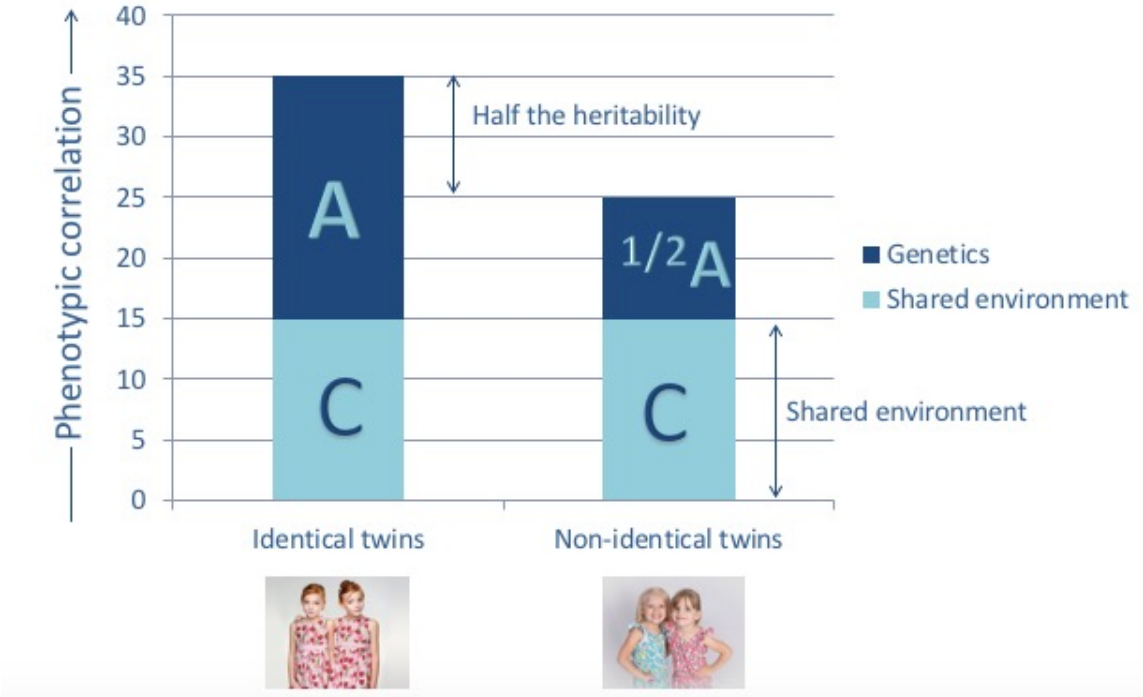
When someone tells you that height is 80% heritable, does that mean:

a) *80% of the variation within the population on the trait of height is due to variation of the genes?*

b) 80% of the reason you are the height you are is due to genes ?

Answer:

ANSWER A: 80% of the variation within the population on the trait of height is due to variation of the genes



Heritability:

1) Population Based

$$h^2 = \frac{\sigma_G^2}{\sigma_P^2}$$

2) = correlation between phenotypic variation and genotypic variation

3) = how well can genetic variation work as a proxy for phenotypic variation

4) used in reference to continuous or quantitative traits

5) example, height, I.Q., fingerprint ridge count

6) subject to the independent action of numerous variables of small effect

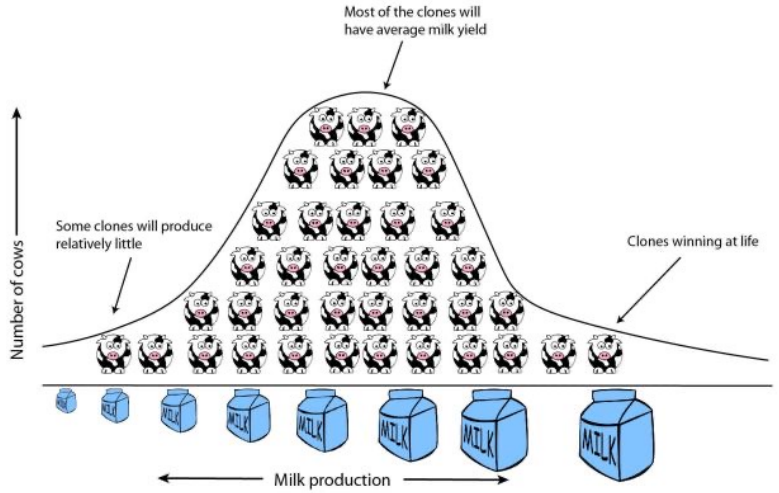
7) subject to the **Central LIMIT THEOREM** central limit theorem and exhibit an *approximate* ***GAUSSIAN DISTRIBUTION*** (the "Bell Curve")

Easier to think in terms of something being "more genetic" or "less genetic" is what "more heritable" or "less heritable"

Heritability = Non Constant

Lactation milk yield in dairy cattle nearly doubled from approximately 25% in the 1970s to roughly 40% in recent times.

Heritability can change over time because the variance in genetic values can change, the variation due to environmental factors can change, or the correlation between genes and environment can change.



Genetic Variance

Genetic variance can change if

1) allele frequencies change (e.g., due to selection or inbreeding),

2) if new variants come into the population (e.g., by migration or mutation),

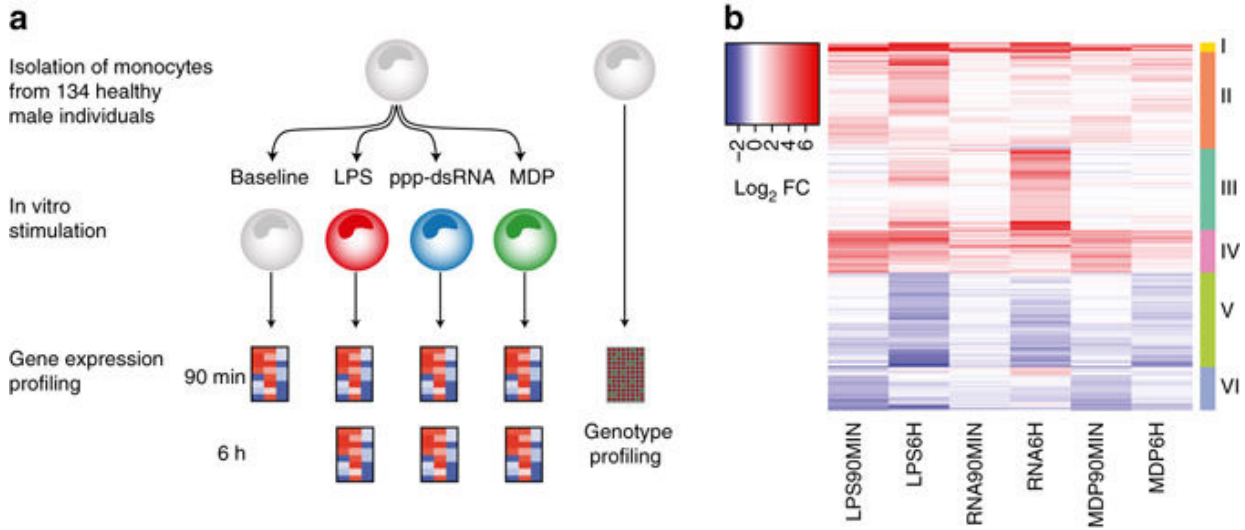
or

3) if existing variants only contribute

to genetic variance following a change

in genetic background or

the environment.



Variance

The same trait measured over an individual's lifetime may have different genetic and environmental effects influencing it, such that the variances become a function of age.

Ex:

variance in weight at birth influenced by maternal uterine environment, and variance in weight at weaning depends on maternal milk production,

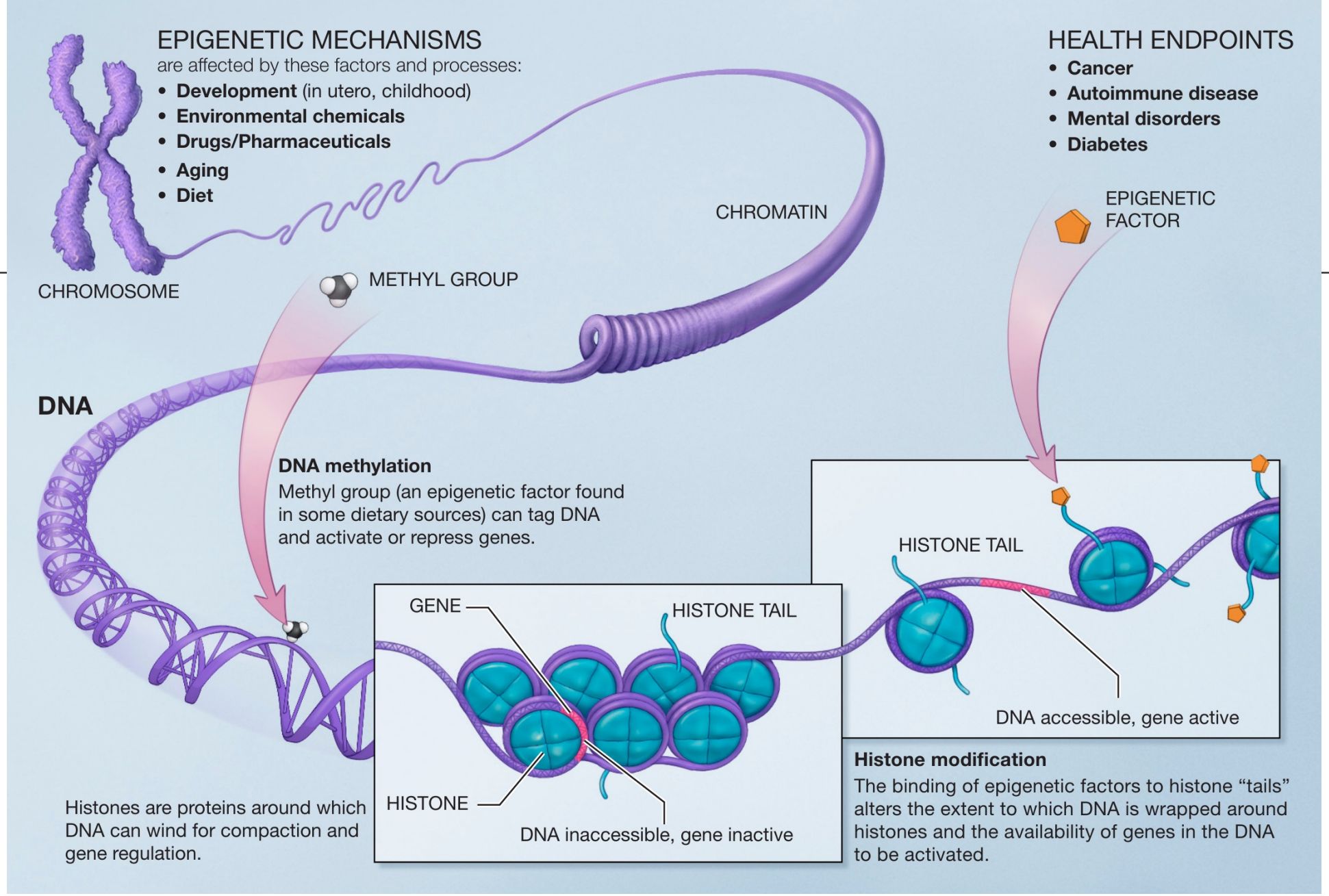
but

variance of mature adult weight is unlikely to be influenced by maternal factors, which themselves have both a genetic and environmental component.

Manipulating Heritability

Heritabilities may be manipulated by changing the variance contributed by the environment.

------- >>>>>> EPIGENETICS


EPIGENETIC MECHANISMS
are affected by these factors and processes:
• Development (in utero, childhood)
• Environmental chemicals
• Drugs/Pharmaceuticals
• Aging
• Diet
HEALTH ENDPOINTS
• Cancer
• Autoimmune disease
• Mental disorders
• Diabetes
CHROMOSOME
CHROMATIN
METHYL GROUP
EPIGENETIC FACTOR
DNA
DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.
GENE
HISTONE TAIL
HISTONE
DNA inaccessible, gene inactive
HISTONE TAIL
DNA accessible, gene active
Histones are proteins around which DNA can wind for compaction and gene regulation.
Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

Epigenetic Changes

Examples of mechanisms that produce such changes which alter how genes are expressed (without changing underlying DNA) are:

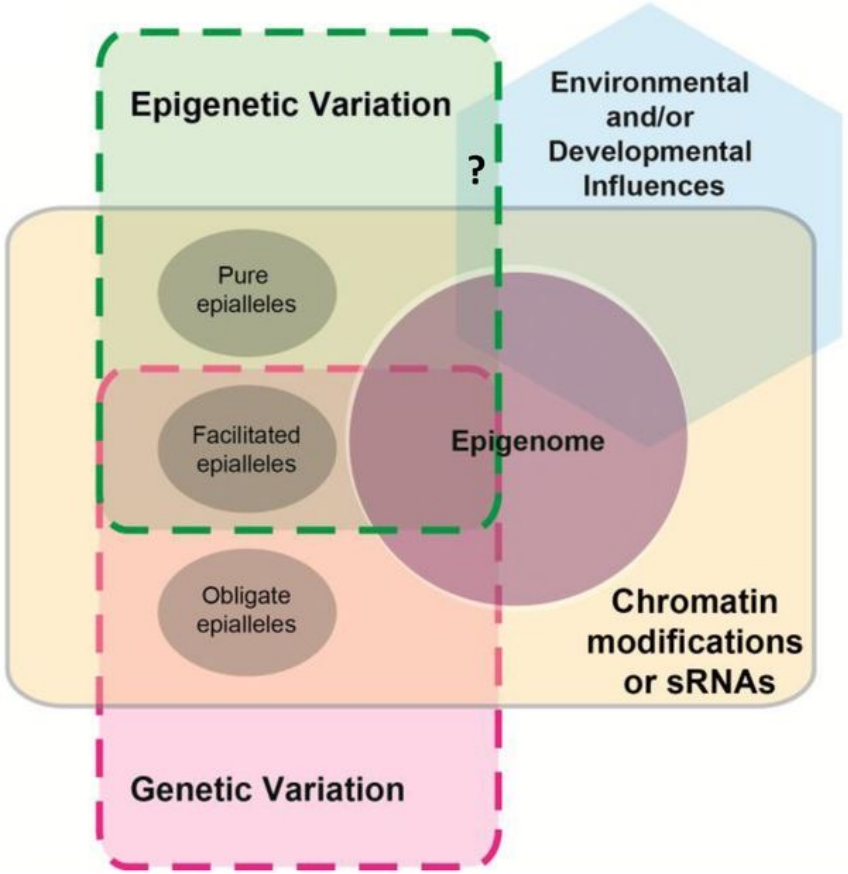
- DNA methylation
- Histone modification
- Parmutations
- Bookmarking
- Imprinting
- Gene Silencing
- X Chromosome inactivation
- Positron effect
- DNA methylation reprogramming
- Transvection
- Maternal effects
- The progress of carcinogenesis
- Many effects of teratogens
- Regulation of histone modifications and hemochromatin
- Parthenogenesis & cloning

Gene expression can be controlled through the action of REPRESSOR PROTEINS that attach to the “silencer” regions of the

Lifecycle Epigenetic Changes

- May last through cell divisions for the duration of the cell's life
- May also last for multiple generations
- Do not require the involvement of changes in the underlying DNA sequence of the organism

TYPES of Epigenetic Changes



Epigenetic variation: Heritable differences that are independent of changes in DNA sequence

Chromatin modifications: Differences in the presence or types of histones (variants) and modifications of DNA (methylation) or histones (methylation, acetylation, etc) and small RNAs that are often associated with epigenetic variation but can be influenced by genetic variation or development / environment

Epigenome: The genome-wide distribution of chromatin modifications or DNA methylation patterns that may include non-heritable changes or genetically influenced patterns

Epialleles: Meiotically heritable allelic differences in chromatin state

Pure epialleles: Epialleles that have differences in chromatin state that are independent of any genetic information

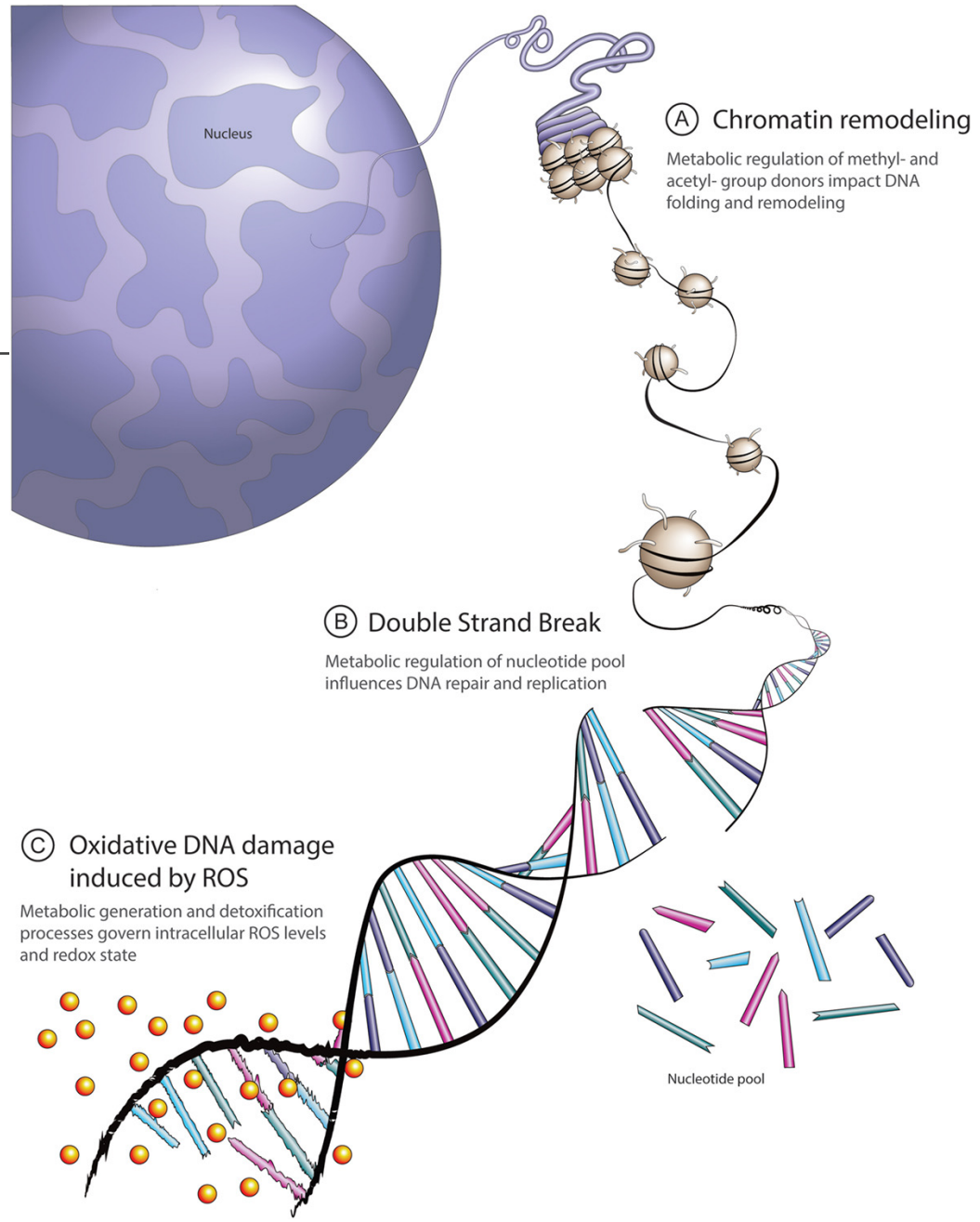
Facilitated epialleles: Epialleles for which a genetic difference (i.e. transposon insertion) leads to the potential to adopt alternate chromatin states

Obligate epialleles: Epialleles with altered chromatin state that is fully dependent upon genetic variants (either cis or trans-acting changes)

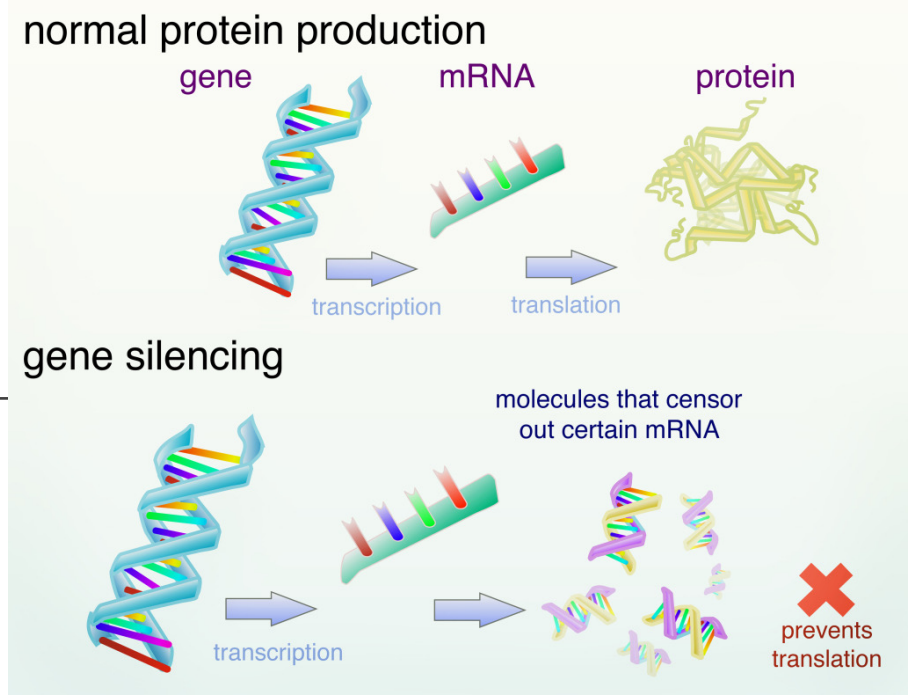
DNA DAMAGE

Very frequent, occurring on average about 60,000 times a day per cell of the human body

Largely repaired, but at the site of repair, epigenetic changes can remain



Gene Silencing



Caused by a **double strand break in DNA**

Causes DNA methylation

Promotes silencing types of histone modifications **(chromatin remodeling)**

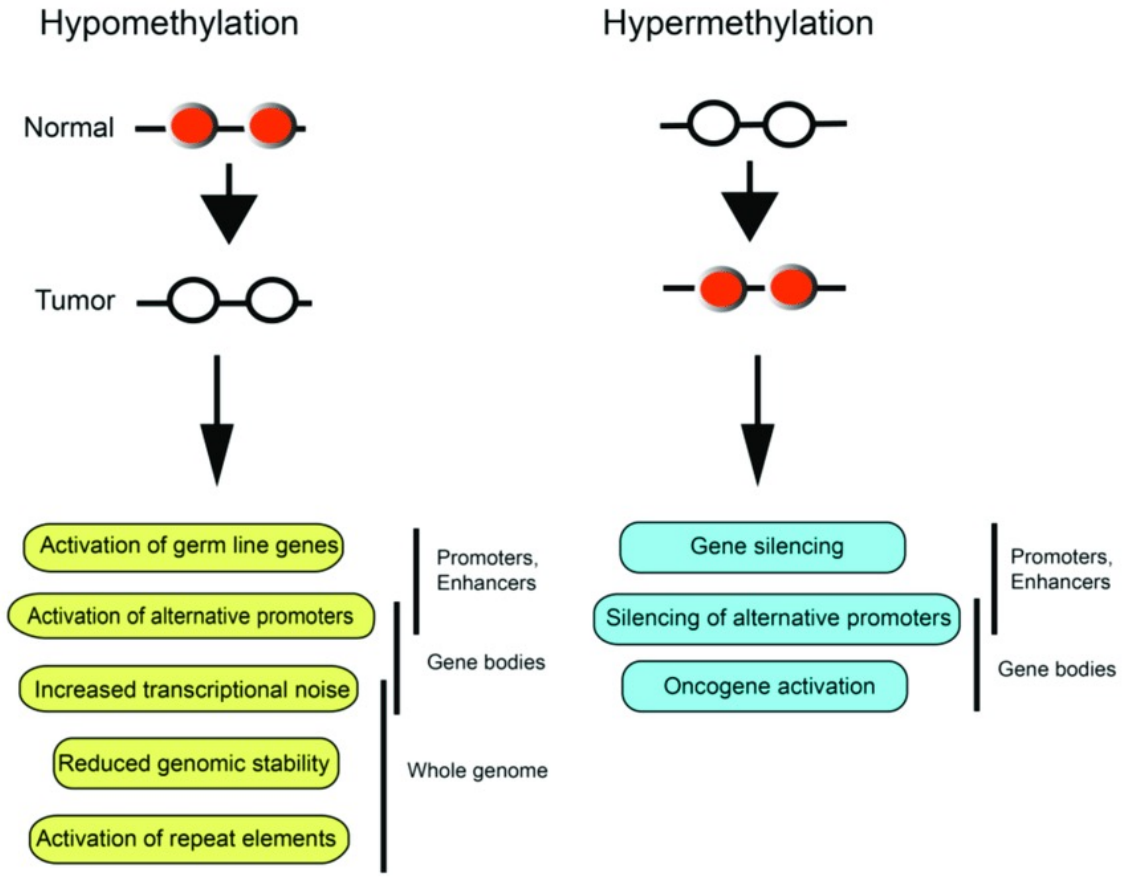
Parp1 (poly(ADP)-ribose polymerase) and is product poly(ADP)-ribose (PAR) accumulate at repair ---> directs recruitment and activation of the chromatin remodeling protein ALC1 that can cause **nucleosome remodeling.**

- found to cause, for instance, epigenetic silencing of DNA repair gene MLH1

Hypomethylation

Caused through the activation of oxidative stress pathways

DNA damaging chemicals: benzene, hydroquinone, styrene, carbon, tetrachloride, and trichloroethylene



Foods

Some Increase the levels of DNA repair enzymes such as **MGMT** and **MLH1** and **p53**.

Other food components can reduce DNA damage, such as soy **isoflavones.**

- In one study, markers for oxidative stress were decreased by a 3-week diet supplemented with soy.
- A decrease in oxidative DNA damage was also observed 2 h after consumption of **amthocyanin**-rich **bilberry** (**Vaccinium myrtillius L.) pomace** extract.

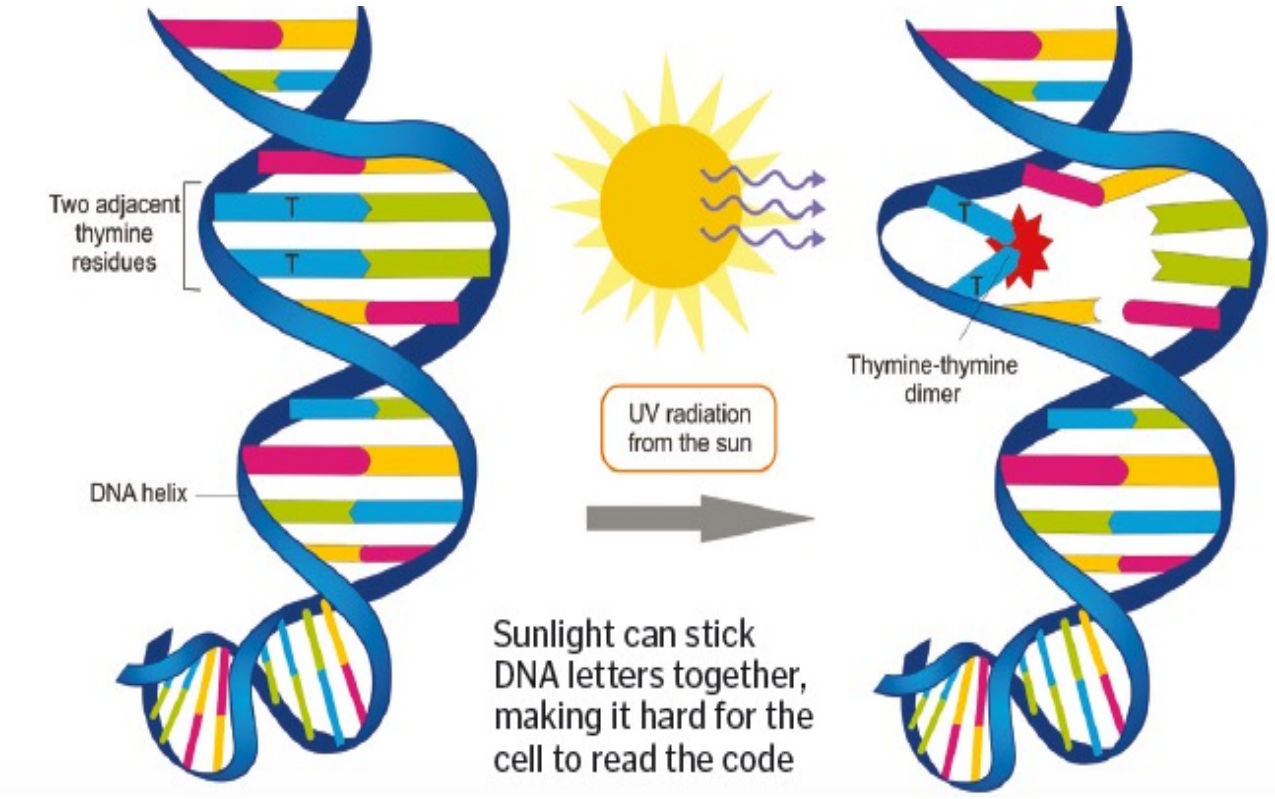
UV Radiation

Common source of **DNA DAMAGE**

CREATES: Cyclobutane-pyrimidine dimers & 6-4 photoproducts (and Dewar valance isomers) ---> the two most abundant mutagenic & cytotoxic DNA lesions

Pathways to repair these lesions:

Excision repair, mutagenic repair, recombinational repair, Cell-cycle checkpoints and apoptosis



Covalent Modifications

Can happen to and are central to the role of epigenetic inheritance:

1) DNA (e.g. cytosine methylation and hydroxymethylation) or

2) histone proteins (e.g. lysine acetylation, lysine and arginine methylation, serine and threonine phosphorylation, and lysine ubiquitination and sumoylation)

Chromatin Regulation:

Chromatin is the complex of DNA and the histone proteins with which it associates.

Transcription States

If the way that DNA is wrapped around the histones changes, gene expression can change as well. Chromatin remodeling is accomplished through two main mechanisms:

1) **Post translational Modification of amino acids** (making up histone proteins)
   - By altering the shape of the histones around them, these modified histones would ensure that a lineage-specific transcription program is maintained after cell division.

2) Addition of **Methyl Groups** to the **DNA at CpG sites** to convert cytoside to 5-methylcytosine
   - DNA is not completely unwound during replication ---> modified histones carried to DNA.

Genetic Imprinting & Methylation

Histones may act as templates, initiating the surrounding new histones to be shaped in the new manner.

5-Methylcytosine performs much like a regular cytosine, pairing with a guanine in double-stranded DNA.

Some areas of genome are methylated more heavily than others, and highly methylated areas tend to be less transcriptionally active, through a mechanism not fully understood.

Methylation of cytosines can also persist from the germ line of one of the parents into the zygote.

Heritability of Histone State

Depends on certain enzymes (such as DNMT1) that have a higher affinity for 5-methylcytosine than for cytosine.

If this enzyme reaches a "hemimethylated" portion of DNA (where 5-methylcytosine is in only one of the two DNA strands) the enzyme will methylate the other half.

Although histone modifications occur throughout the entire sequence, the unstructured N-termini of histones (called histone tails) are particularly highly modified. These modifications include:

- Acetylation, methylation, ubiquitylation phosphorylation, sumoylation, ribosylation, and citrullation.

For example, acetylation of the K14 and K9 lysines of the tail of histone h3 by histone acetyltransferase enzymes (HATs) is known to regulate transcription in accordance with complementary histone deacetylases.[47]

Acetylation

Associated with "active" transcription is biophysical in nature.

Normally has a positively charged nitrogen at its end, lysine can bind the negatively charged phosphates of the DNA backbone.

The acetylation event converts the positively charged amine group on the side chain into a neutral amide linkage.

Removes the positive charge, thus loosening the DNA from the histone. When this occurs, complexes like SWI/SNF and other transcriptional factors can bind to the DNA and allow transcription to occur. This is the "cis" model of the epigenetic function. In other words, changes to the histone tails have a direct effect on the DNA itself.

Histone Tail (“trans model”)

"trans" model. In this model, changes to the histone tails act indirectly on the DNA

For example, lysine acetylation may create a binding site for chromatin-modifying enzymes (or transcription machinery as well).

This chromatin remodeler can then cause changes to the state of the chromatin. Indeed, a bromodomain – a protein domain that specifically binds acetyl-lysine – is found in many enzymes that help activate transcription, including the SWI/SNF complex. It may be that acetylation acts in this and the previous way to aid in transcriptional activation.

Histone Methylation

Methylation of lysine 9 of histone H3 has long been associated with constitutively transcriptionally silent chromatin (constitutive hemotchromatic).

It has been determined that a chromodomain (a domain that specifically binds methyl-lysine) in the transcriptionally repressive protein HP1 recruits HP1 to K9 methylated regions.

One example that seems to refute this biophysical model for methylation is that tri-methylation of histone H3 at lysine 4 is strongly associated with (and required for full) transcriptional activation. Tri-methylation, in this case, would introduce a fixed positive charge on the tail.

Histone Methylation

It has been shown that the histone lysine methyltransferase (KMT) is responsible for this methylation activity in the pattern of histones H3 and H4.

This enzyme utilizes a catalytically active site called the SET domain (Suppressor of variegation, Enhancer of zeste, Trithorax).

The SET domain is a 130-amino acid sequence involved in modulating gene activities. This domain has been demonstrated to bind to the histone tail and causes the methylation of the histone.[49]

DNA Methylation

Occurs in repeated sequences, and helps to suppress the expression and mobility of ‘transoposable elements’

5-methylcytosine = spontaneously deminated to (replacing nitrogen to carbon dioxide) thymidine

DNA methylation

By preferentially modifying hemimethylated DNA, DNMT1 transfers patterns of methylation to a newly synthesized strand after DNA replication, and therefore is often referred to as the ‘maintenance' methyltransferase.

DNMT1 is essential for proper embryonic development, imprinting and X-inactivation

Permanent Genetic Mutation

Epigenetic changes have ability to direct increased frequencies of permanent genetic mutation. DNA methylation patterns are known to be established and modified in response to environmental factors by a complex interplay of at least three independent DNA methyltransferase, DNMT1, DNM3a, and DNMT3B, the loss of any of which is lethal in mice.

Histone Manipulation

Histones H3 and H4 can also be manipulated through demethylation using histone lysine demethylase (KDM).

- JmjC is capable of demethylating mono-, di-, and tri-methylated substrates. Chromosomal regions can adopt stable and heritable alternative states resulting in bistable gene expression without changes to the DNA sequence.

Epigenetic control is often associated with alternative covalent modifications of histones. The stability and heritability of states of larger chromosomal regions are suggested to involve positive feedback where modified nucleosmones recruit enzymes that similarly modify nearby nucleosomes. A simplified stochastic model for this type of epigenetics is found here.

Small interfering RNAs

It has been suggested that chromatin-based transcriptional regulation could be mediated by the effect of small RNAs. Small interfering RNA's can modulate transcriptional gene expression via epigenetic modulation of targeted promotors.

RNA Transcripts

After gene after being turned on, transcribes a product that (directly or indirectly) maintains the activity of that gene.

For example, Hnf4 and MyoD enhance the transcription of many liver-specific and muscle-specific genes, respectively, including their own, through the transcripton factor activity of the proteins they encode.

RNA signaling includes differential recruitment of a hierarchy of generic chromatin modifying complexes and DNA methyltransferases to specific loci by RNAs during differentiation and development.

Other changes

Mediated by the production of different splice forms of RNA, or by formation of double-stranded RNA (RNAi).

Descendants of the cell in which the gene was turned on will inherit this activity, even if the original stimulus for gene-activation is no longer present.

Signal transduction: turns on and off the messages.

MicroRNAs

MicroRNAs

MicroRNAs (miRNAs) are members of non-coding RNAs that range in size from 17 to 25 nucleotides.

miRNAs regulate a large variety of biological functions in plants and animals.

It appears that about 60% of human protein coding genes are regulated by miRNAs. Many miRNAs are epigenetically regulated. About 50% of miRNA genes are associated with CpG islands, that may be repressed by epigenetic methylation.

Transcription from methylated CpG islands is strongly and heritably repressed.Other miRNAs are epigenetically regulated by either histone modifications or by combined DNA methylation and histone modification.

mRNA

mRNA

Methylation of mRNA plays a critical role in human energy homeostasis.

The obesity-associated FTO gene is shown to be able to demethylate N6-methyladenosine in RNA.

sRNAs

sRNAs

Small (50–250 nucleotides), highly structured, non-coding RNA fragments found in bacteria.

Control gene expression including virulence genes in pathogens and are viewed as new targets in the fight against drug-resistant bacteria.

They play an important role in many biological processes, binding to mRNA and protein targets in prokaryotes.

Their phylogenetic analyses, for example through sRNA–mRNA target interactions or protein binding properties, are used to build comprehensive databases. sRNA- gene maps based on their targets in microbial genomes are also constructed.

Prions

Infectious forms of proteins.

Ability to catalytically convert other native state versions of the same protein to an infectious conformational state.

Can be viewed as epigenetic agents capable of inducing a phenotypic change without a modification of the genome

Fungal prions

Can be inherited without modification of the genome

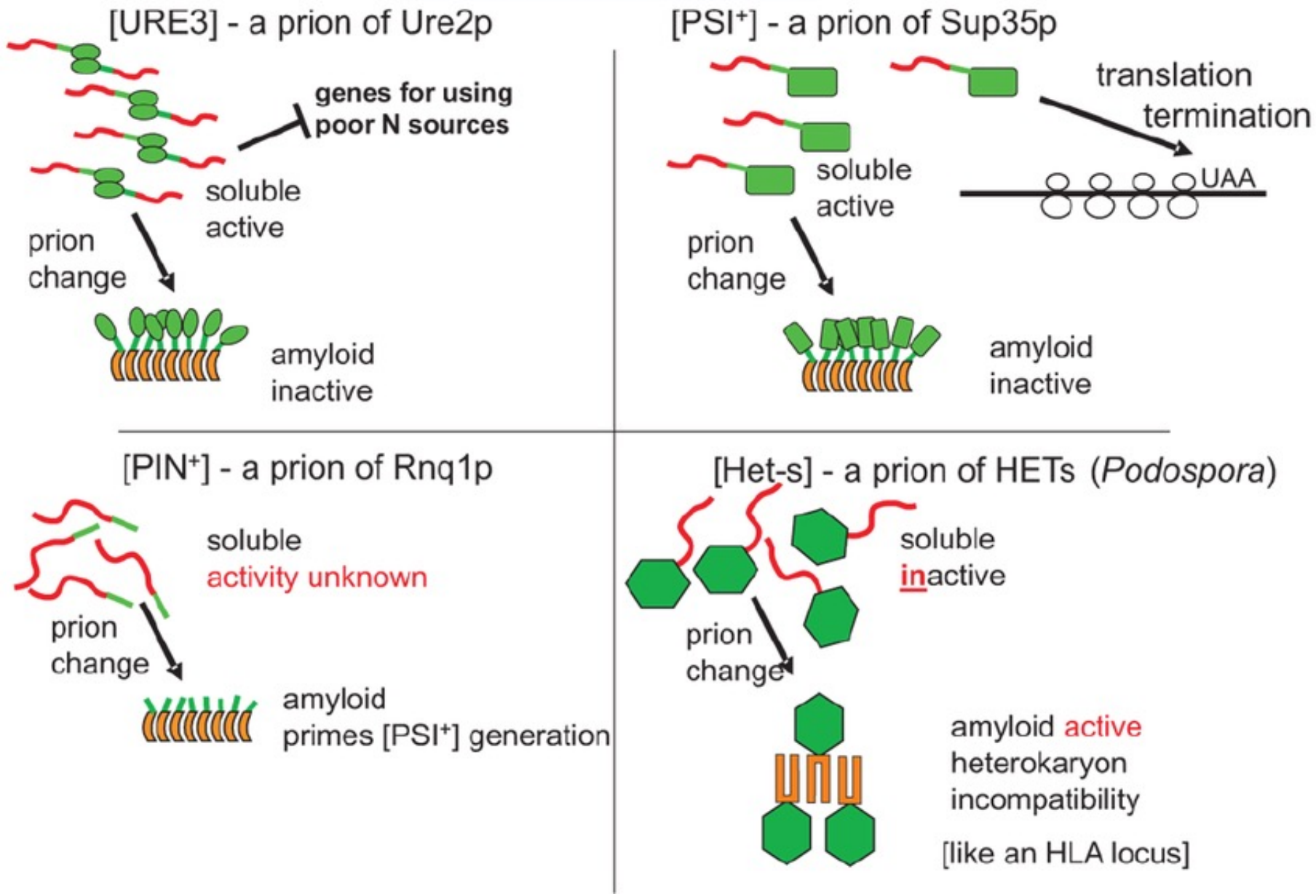
PSI+and URE3, are the two best studied

Can have a phenotypic effect through the sequestration of protein in aggregates, thereby reducing that protein's activity.

In PSI+ cells, the loss of the Sup35 protein (which is involved in termination of translation) causes ribosomes to have a higher rate of read-through of stop codons, an effect that results in suppression of nonsense mutations in other genes.

The ability of Sup35 to form prions may be a conserved trait. It could confer an adaptive advantage by giving cells the ability to switch into a PSI+ state and express dormant genetic features normally terminated by stop codon mutations.

Yeast and Fungal Prions



Structural Inheritance

In Ciliates such as Tetrahymena and Paramecium, genetically identical cells show heritable differences in the patterns of ciliary rows on their cell surface.

Experimentally altered patterns can be transmitted to daughter cells. It seems existing structures act as templates for new structures. The mechanisms of such inheritance are unclear, but reasons exist to assume that multicellular organisms also use existing cell structures to assemble new ones

Nucleosome Poisoning

Eukaryotic genomes have numerous nucleosomes.

Nucleosome position is not random, and determine the accessibility of DNA to regulatory proteins.

Promoters active in different tissues have been shown to have different nucleosome positioning features. This determines differences in gene expression and cell differentiation. It has been shown that at least some nucleosomes are retained in sperm cells (where most but not all histones are replaced by protamines). Thus nucleosome positioning is to some degree inheritable. Recent studies have uncovered connections between nucleosome positioning and other epigenetic factors, such as DNA methylation and hydroxymethylation.[90]

Functions and consequences - Development

Development

Developmental epigenetics can be divided into predetermined and probabilistic epigenesis.

- Probabalistic epigenetics
  - bidirectional structure-function development with experiences and external molding development.
- Predetermined epigenesis is a unidirectional movement
  - Structural development in DNA ---->t he functional maturation of the protein.
  - "Predetermined" here means that development is scripted and predictable. Probabilistic epigenesis on the other hand is a bidirectional structure-function development with experiences and external molding development.
- Somatic epigenetic inheritance, particularly through DNA and histone covalent modifications and nucleosome repositioning, is very important in the development of multicellular eukaryotic organisms.[90]

Epigenetics in bacteria

While epigenetics is of fundamental importance in eukaryotes (especially metazoans), different in bacteria.

Bacteria make use of **postreplicative DNA methylation** for the epigenetic control of DNA-protein interactions.

Bacteria also use DNA **adenine methylation** (rather than DNA cytosine methylation) as an epigenetic signal.

Medicine

Epigenetics has many and varied potential medical applications.[128] In 2008, the National Institutes of Health announced that $190 million had been earmarked for epigenetics research over the next five years. In announcing the funding, government officials noted that epigenetics has the potential to explain mechanisms of aging, human development, and the origins of cancer, heart disease, mental illness, as well as several other conditions. Some investigators, like Randy Jirtle, Ph.D., of Duke University Medical Center, think epigenetics may ultimately turn out to have a greater role in disease than genetics.

Geonomic Imprinting

A phenomenon in mammals where the father and mother contribute different epigenetic patterns for specific genomic loci in their germ cells.

The best-known case of imprinting in human disorders is that of Angelman syndrome and Prader-Willi Syndrome – both can be produced by the same genetic mutation, chromosome 15g partial deletion., and the particular syndrome that will develop depends on whether the mutation is inherited from the child's mother or from their father. This is due to the presence of genomic imprinting in the region. Beckwith-Wiedmann syndrome. is also associated with genomic imprinting, often caused by abnormalities in maternal genomic imprinting of a region on chromosome 11.

Rett syndrome is underlain by mutations in the MECP2 gene despite no large-scale changes in expression of MeCP2 being found in microarray analyses. BDNF is downregulated in the MECP2 mutant resulting in Rett syndrome.

Cancer

Epigenetic alterations of DNA repair genes or cell cycle control genes are very frequent in sporadic (non-germ line) cancers, being significantly more common than germ line (familial) mutations in these sporadic cancers.

Epigenetic alterations are important in cellular transformation to cancer, and their manipulation holds great promise for cancer prevention, detection, and therapy.[Several medications which have epigenetic impact are used in several of these diseases. These aspects of epigenetics are addressed in cancer epigenetics.

Aging

The aging phenotype—marked by functional decline of tissues and organs—is owed in large part to a changing epigenetic landscape. Specifically, changes in the methylation state of DNA has the consequence of perpetuating the aging phenotype, along with histone modifications, chromatin remodeling, and non-coding RNA misregulation. After research began revealing the substantial role epigenetics plays in creating the aging phenotype and promoting age-associated disease, a host of scientists globally have devoted themselves to finding potential interventions to the aging process that capitalize on these epigenetic markers. Furthermore, reduced methylation of DNA with age also functions simultaneously with higher variability in methylation sites—a finding that is particularly well visualized by looking at the epigenomes of monozygotic twins.[

Examples of drugs altering gene expression from epigenetic events

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The use of beta-lactam antibiotics can alter glutamate receptor activity and the action of cyclosporine on multiple transcription factors. Additionally, lithium can impact autophagy of aberrant proteins, and opioid drugs via chronic use can increase the expression of genes associated with addictive phenotypes.[148]

Psychology and psychiatry

Early Life Stress

Cohort of over one-thousand subjects assessed multiple times from preschool to adulthood, subjects who carried one or two copies of the short allele of the serotonin transporter promoter polymorphism exhibited higher rates of adult depression and suicidality when exposed to childhood maltreatment when compared to long allele homozygotes with equal early life stress exposure.

Parental Nutriton

Parental nutrition, in utero exposure to stress, male-induced maternal effects such as the attraction of differential mate quality, and maternal as well as paternal age, and offspring gender could all possibly influence whether a germline epimutation is ultimately expressed in offspring and the degree to which intergenerational inheritance remains stable throughout posterity.

Addiction

Addiction

Addiction is a disorder of the brain's reward system which arises throughtranscriptional & neuroepigenetic and occurs over time from chronically high levels of exposure to an addictive stimulus (e.g., morphine, cocaine, sexual intercourse, gambling, etcTransgenerational epigenetic inheritance of addictive has been noted to occur in preclinical studies.

Anxiety

Transgenerational epigenetic inheritance of anxiety-related phenotypes has been reported in a preclinical study using mice.

In this investigation, transmission of paternal stress-induced traits across generations involved small non-coding RNA signals transmitted via the male germline.

Depression

Epigenetic inheritance of depression-related phenotypes has also been reported in a preclinical study. Inheritance of paternal stress-induced traits across generations involved small non-coding RNA signals transmitted via the paternal germline.

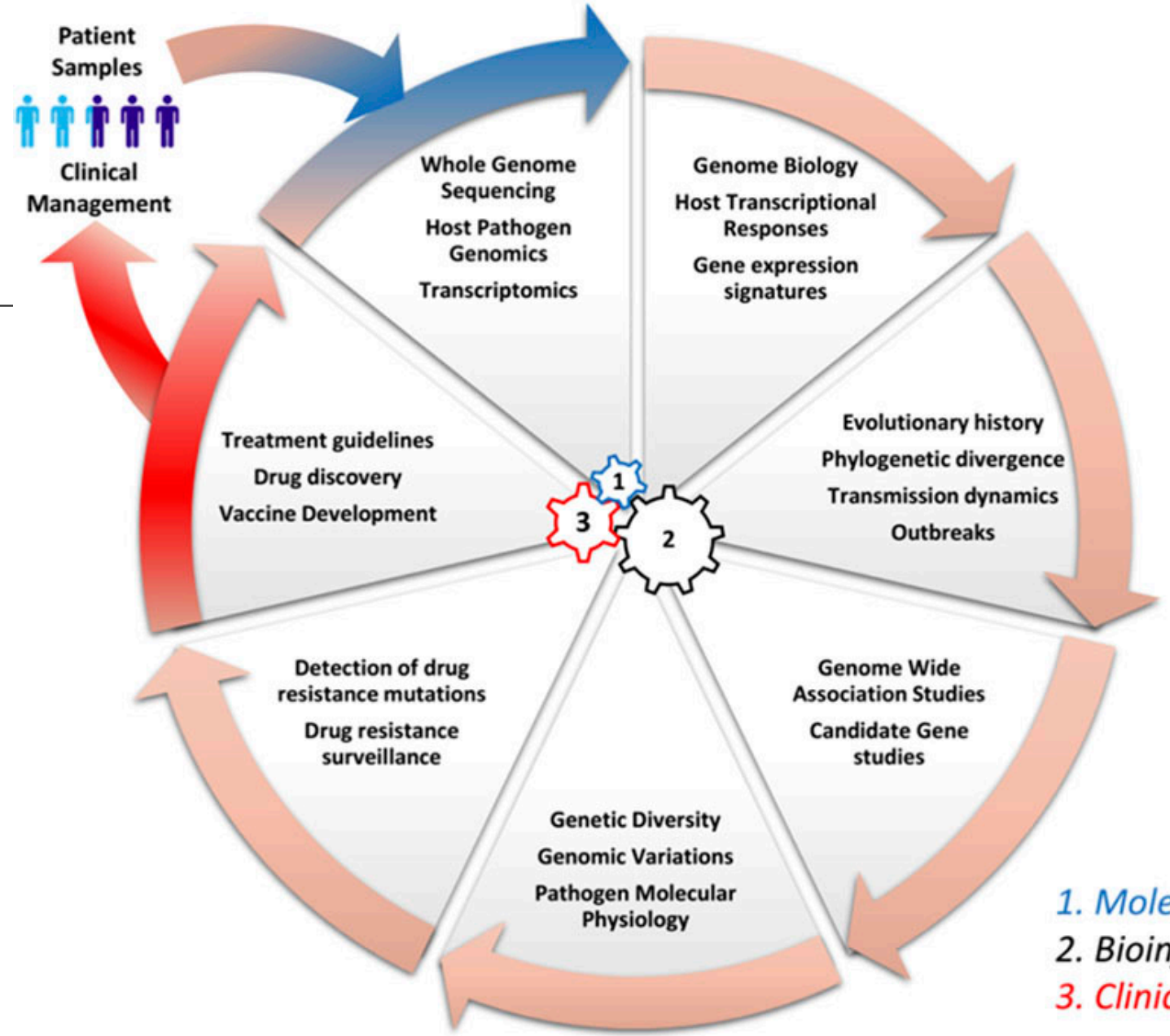
Fear Conditions

Studies on mice have shown that certain conditional fears can be inherited from either parent.

- In one example, mice were conditioned to fear a strong scent, acetophenone, by accompanying the smell with an electric shock.
- Consequently, the mice learned to fear the scent of acetophenone alone. It was discovered that this fear could be passed down to the mice offspring. Despite the offspring never experiencing the electric shock themselves the mice still displayed a fear of the acetophenone scent, because they inherited the fear epigenetically by site-specific DNA methylation. These epigenetic changes lasted up to two generations without reintroducing the shock.[

What is Epigenetics?

SciShow: Epigenetics



1. Molecular Techniques

2. Bioinformatics Applications

3. Clinical Application

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