

Epigenetics, Environment and Human Health

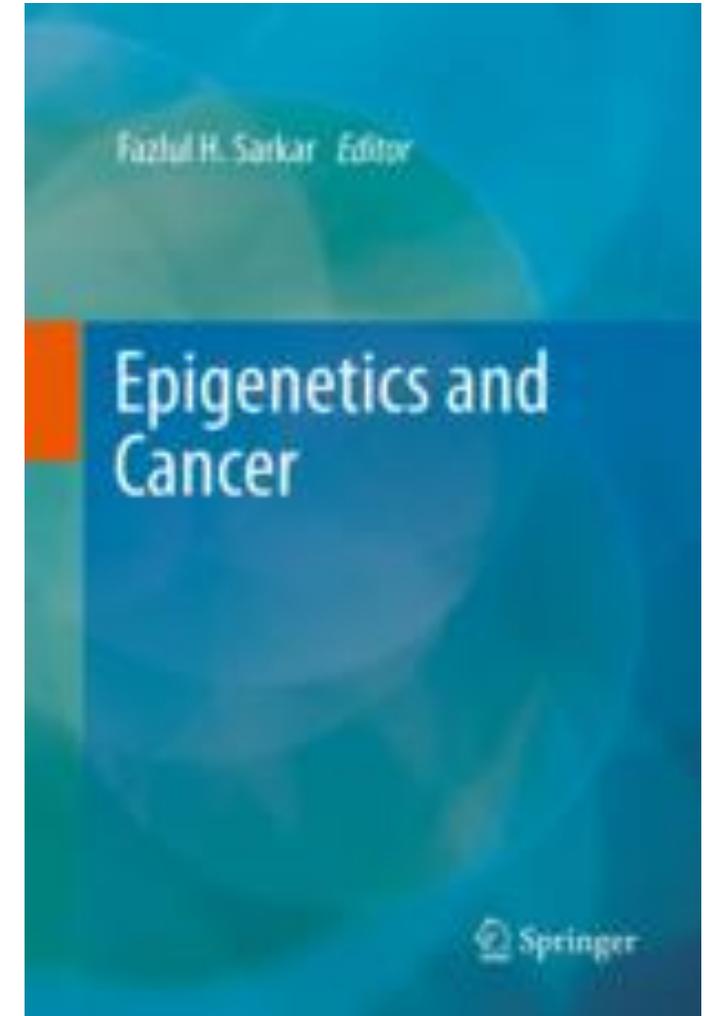
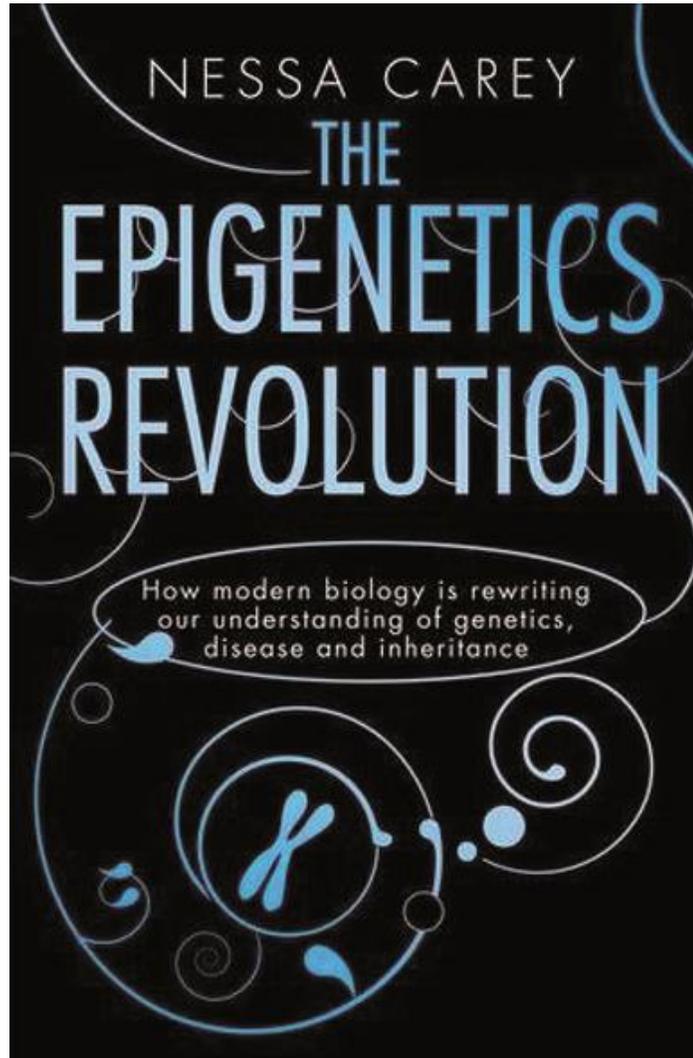
A. Karim Ahmed

*National Council for Science and the Environment
Washington, DC*

May, 2015

Epigenetics

A New Biological Paradigm...



A Question about Cells:

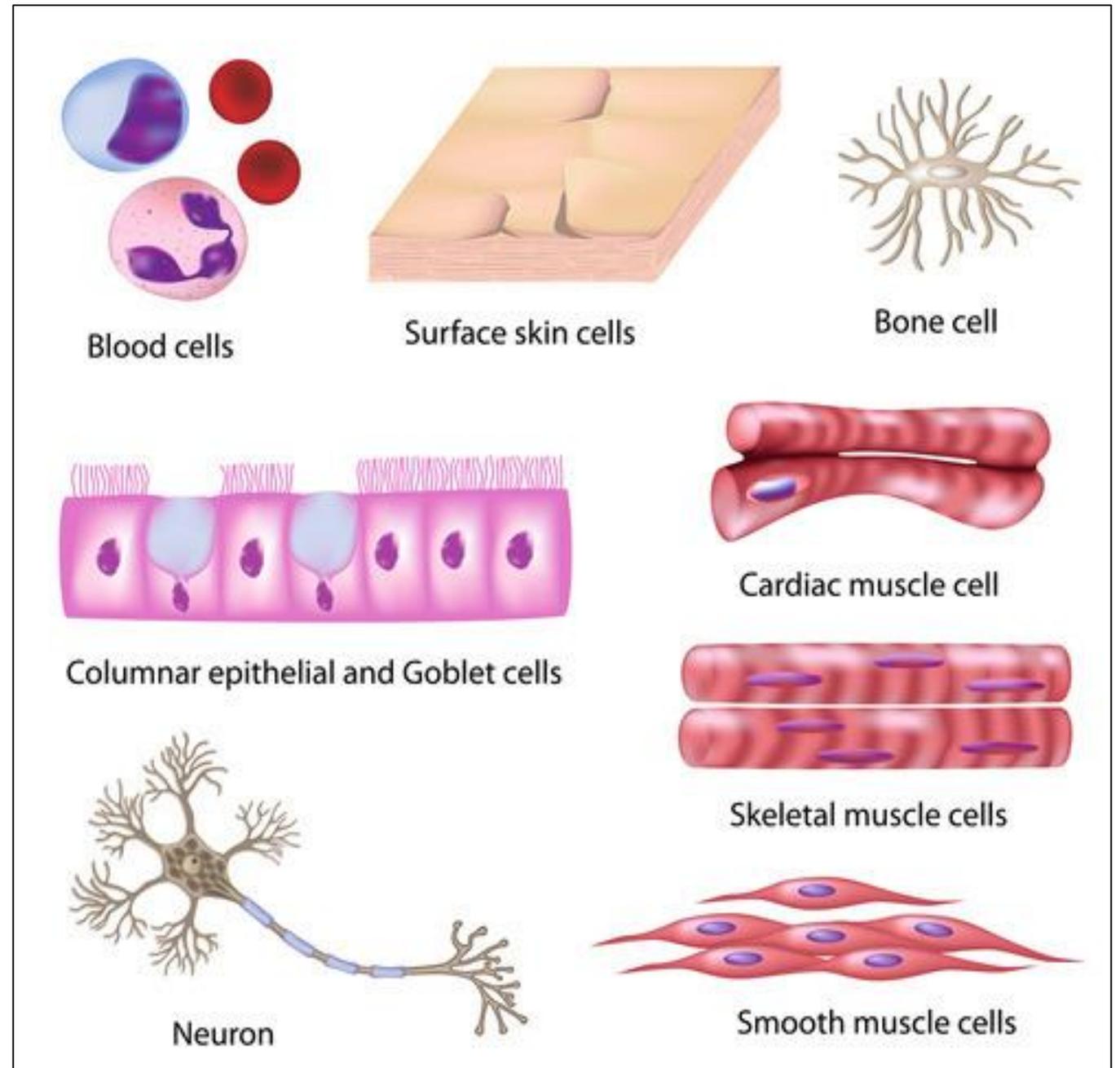
All cells of an individual organism contain the **same genes**. Yet they are **markedly different** from each other. For instance, a skin cell is not the same as a muscle cell, a red blood cell, a nerve cell or a bone cell.

Why is this so?

Answer:

While all cells of an individual possess the same genes, they do not all express them in the same way. There are internal control mechanisms in the cells that **either allow or disallow the expression of certain genes**, leading to different cell types.

This mechanism of cellular differentiation is the **basis** of our current understanding of **epigenetics...**



The Epigenetic Phenomena...

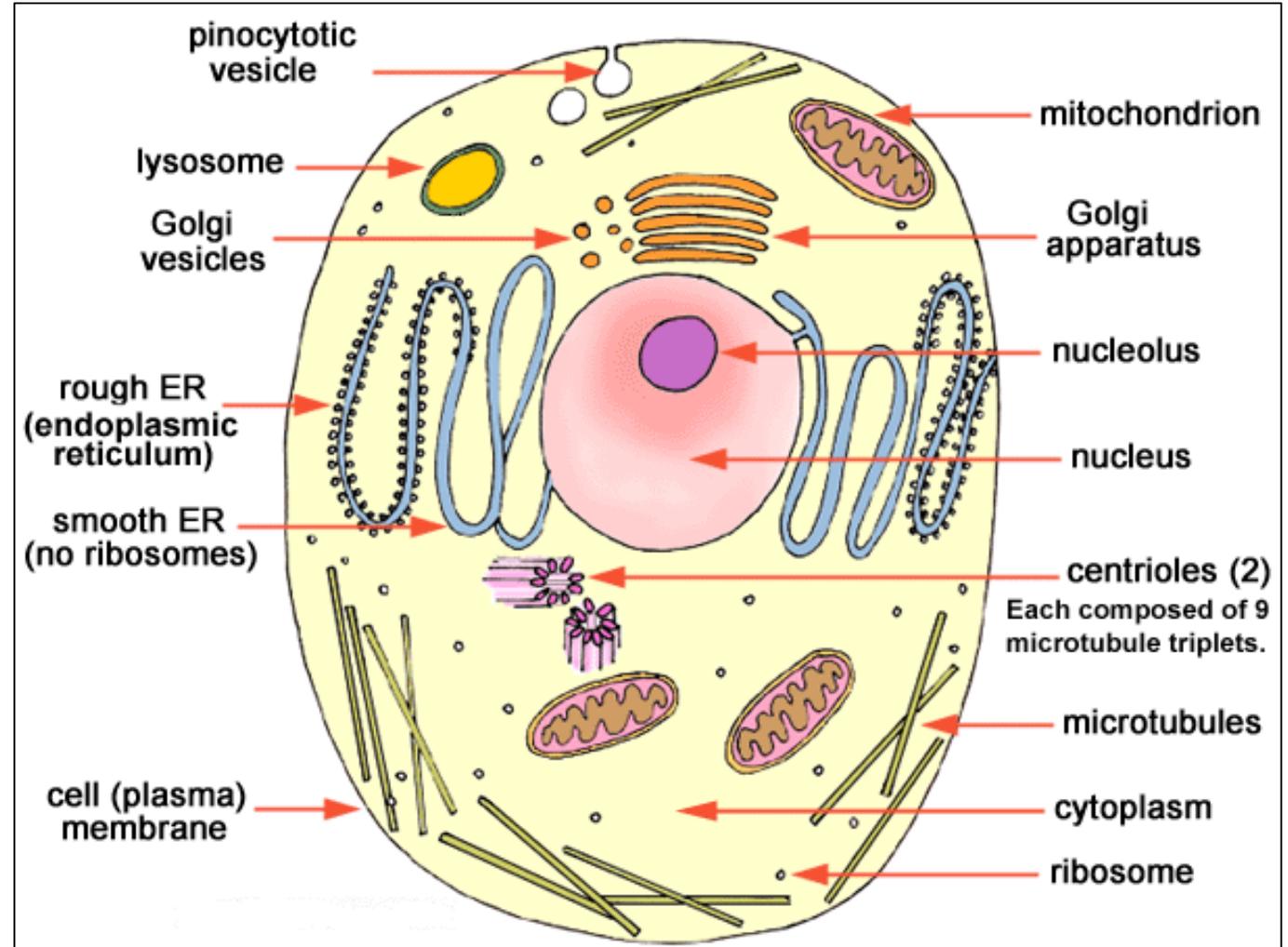
From *Nature Review Genetics*, 13:97 – 109 (2012)

- Epigenetic phenomena in animals and plants are mediated by DNA methylation and stable chromatin modifications. There has been considerable interest in whether **environmental factors modulate** the establishment and maintenance of epigenetic modifications, and could thereby influence gene expression and phenotype.
- **Chemical pollutants, dietary components, temperature changes and other external stresses can indeed have long-lasting effects on development, metabolism and health, sometimes even in subsequent generations.**
- Although the underlying mechanisms remain largely unknown, particularly in humans, **mechanistic insights are emerging** from experimental model systems. These have implications for structuring future research and understanding disease and development.

Components of a Mammalian Cell

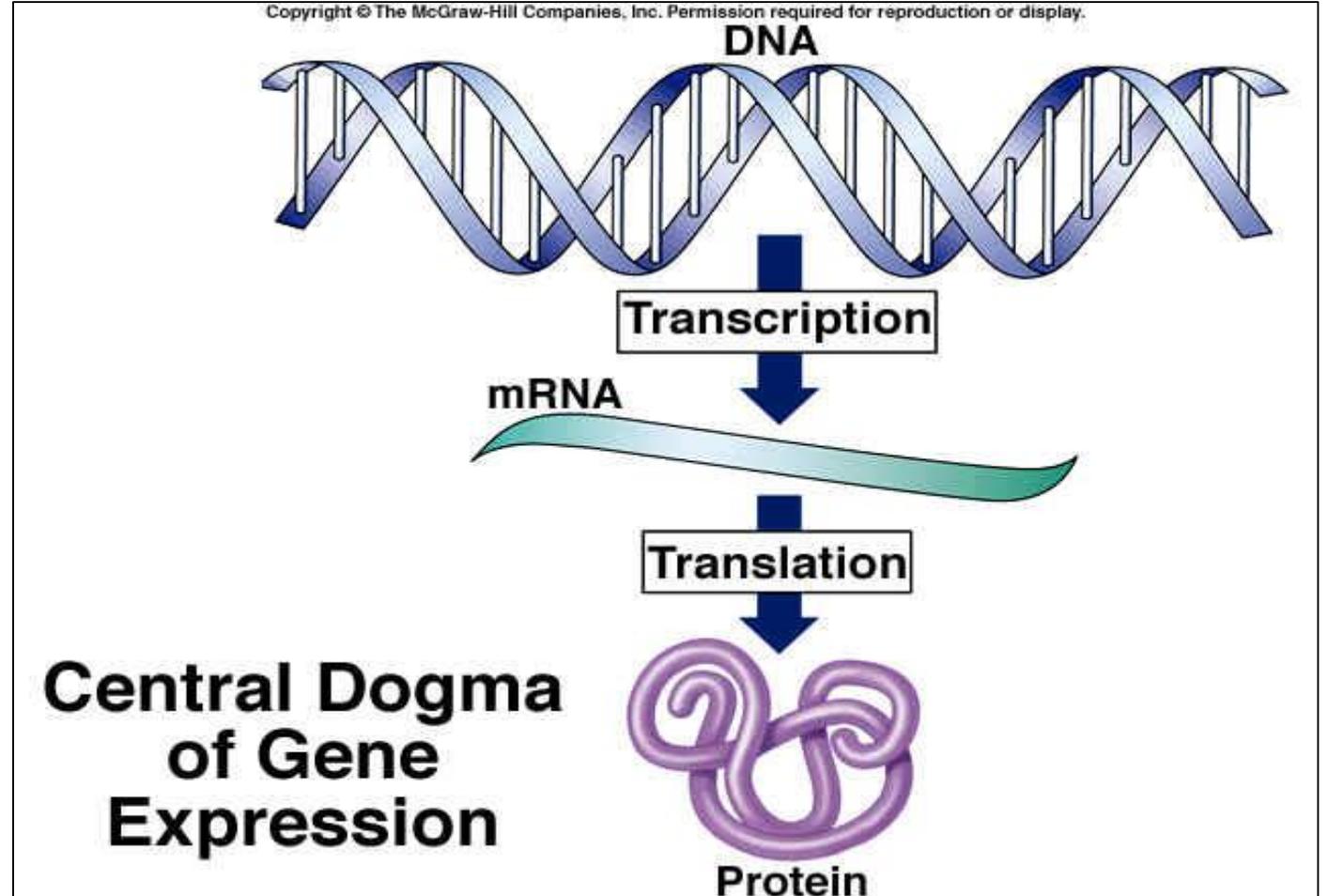
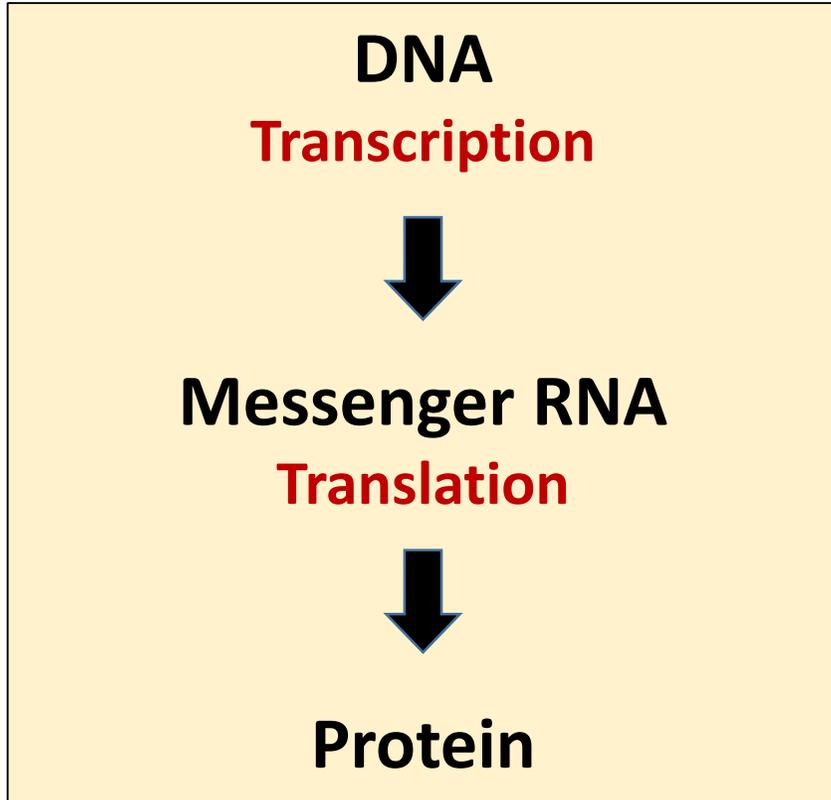
The Phenotypic Expression of a Cell's Gene Involves a Large Supporting Cast of Organelles...

- Cell Membrane
- Nucleus (**diploid genes**)
- Nucleolus
- Mitochondrion (**haploid maternal genes**)
- Ribosome
- Endoplasmic reticulum
- Golgi apparatus
- Lysosome
- Microtubules
- Centrioles
- Pinocytotic vesicle



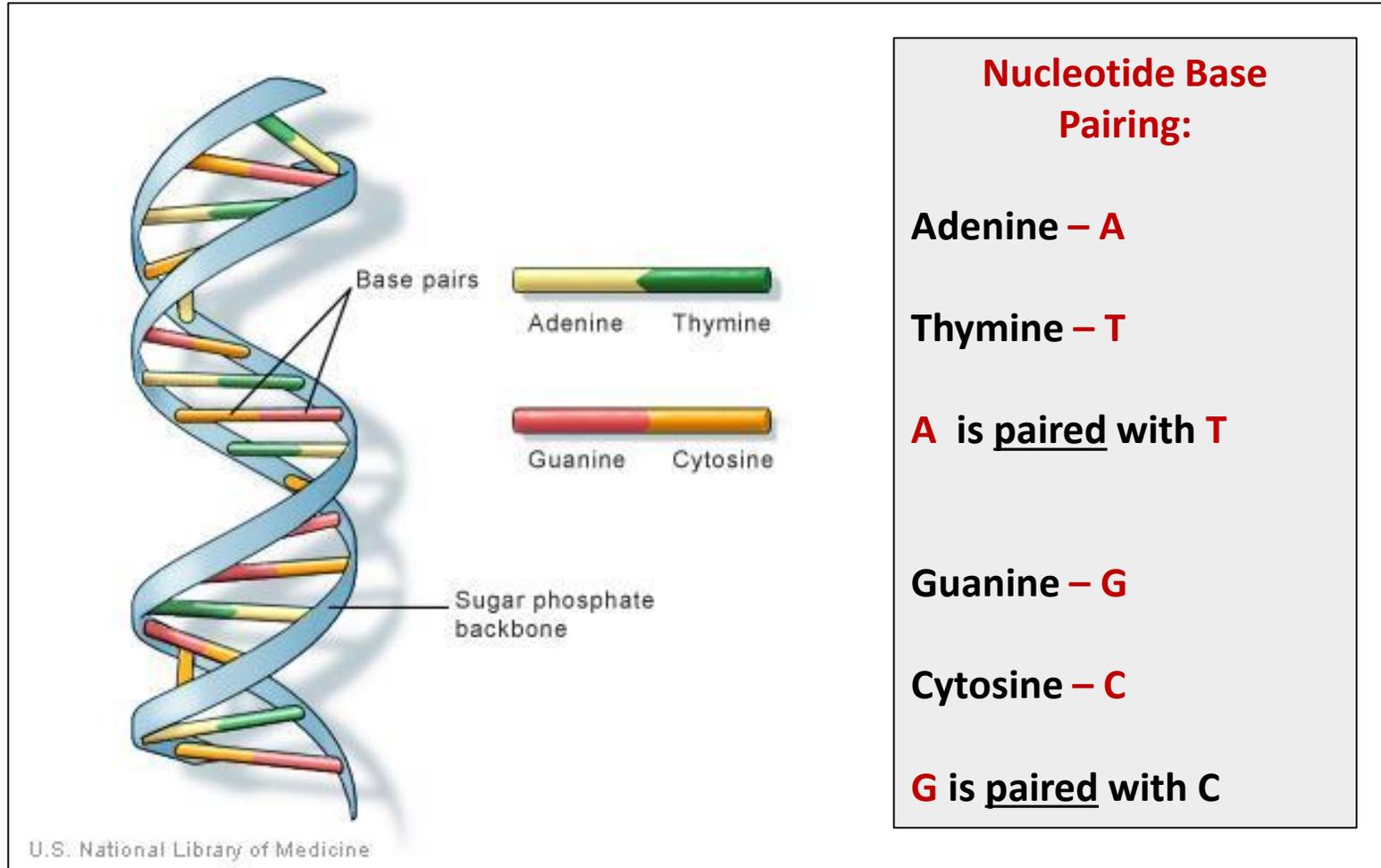
Gene Expression - The Conventional View

A One-Way Street: DNA → Protein Synthesis *via* m-RNA



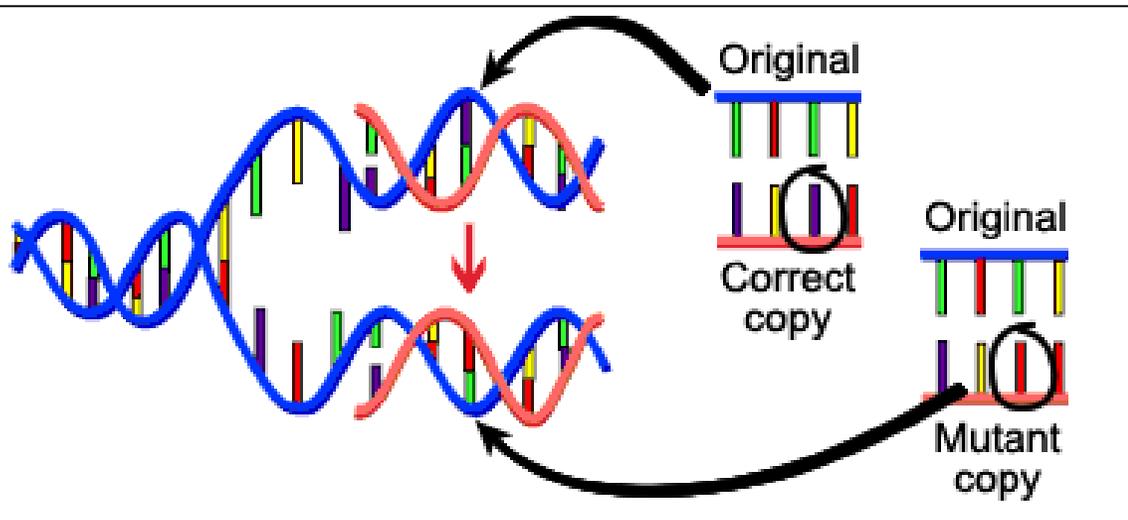
Genes are Composed of Strands of Double-Helical DNA molecule

DNA consists of 4 Nucleotide Bases that are paired to each other: A – T, C – G



Conventional Mechanisms of Gene Mutations of DNA Base-Pairs:

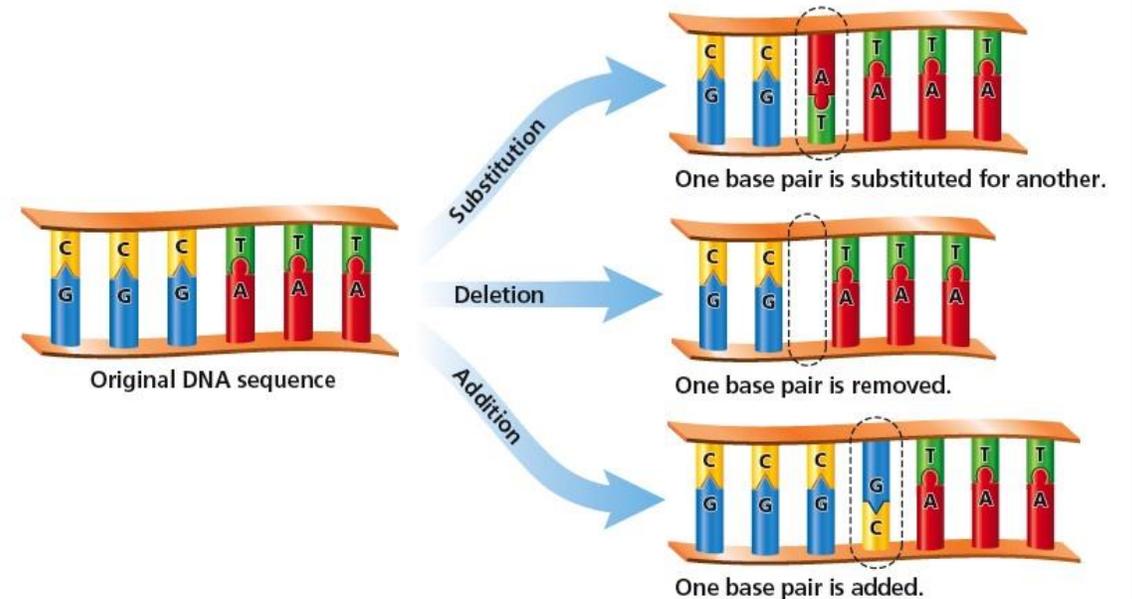
- Base-Pair Substitution (e.g., A – T → C – G)
- Base-Pair Deletion (e.g., minus A – T)
- Base-Pair Addition (e.g., plus C – G)



Point Mutations & Frame-Shift Mutations

7.50

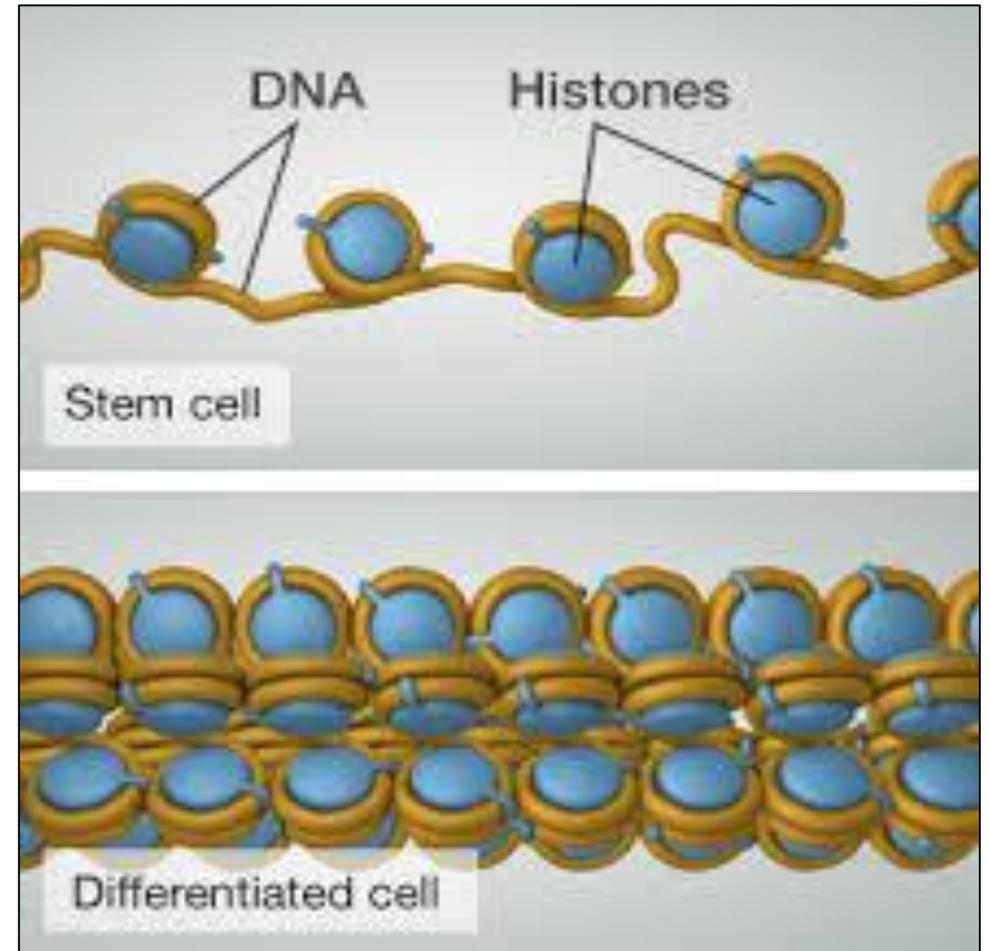
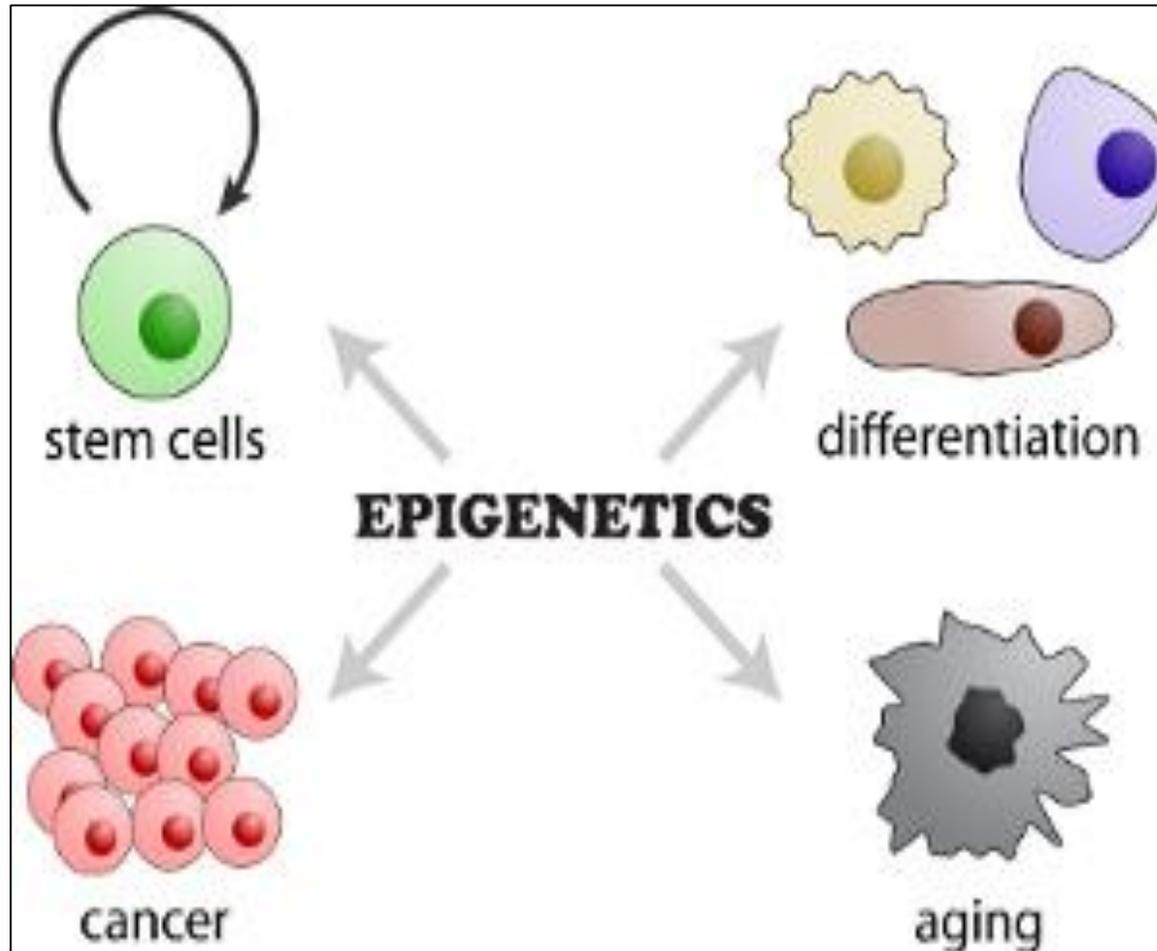
Mutations in Genes



How is the Epigenetic Phenomenon Manifested?

- Epigenetics describes the short-term modification and/or inheritable modification of gene expression rather the permanent mutation of the genetic code in unicellular and multicellular organisms
- Epigenetics occurs by:
 - A developmental cellular differentiation of embryonic stem cells to mature (somatic) cell lines (short-term)
 - A modification of gene expression of the germ cell line over several generations (long-term)

Epigenetics – Different Pathways to Control Gene Expression



Cellular Differentiation (Embryonic)

Fertilized Egg



Blastocyst
(Totipotent)

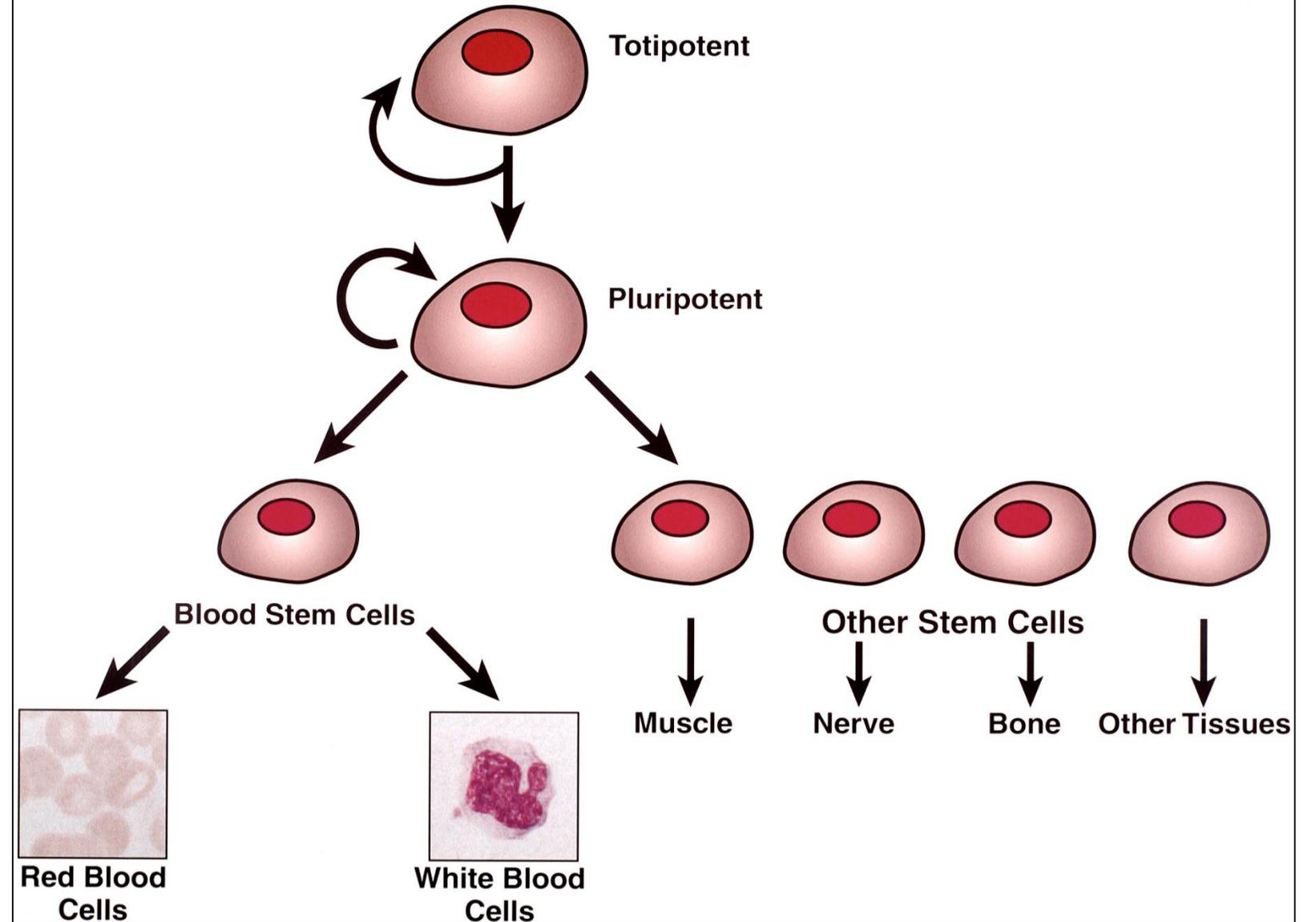


Embryonic Stem Cell
(Pluripotent)



Differentiated Cells

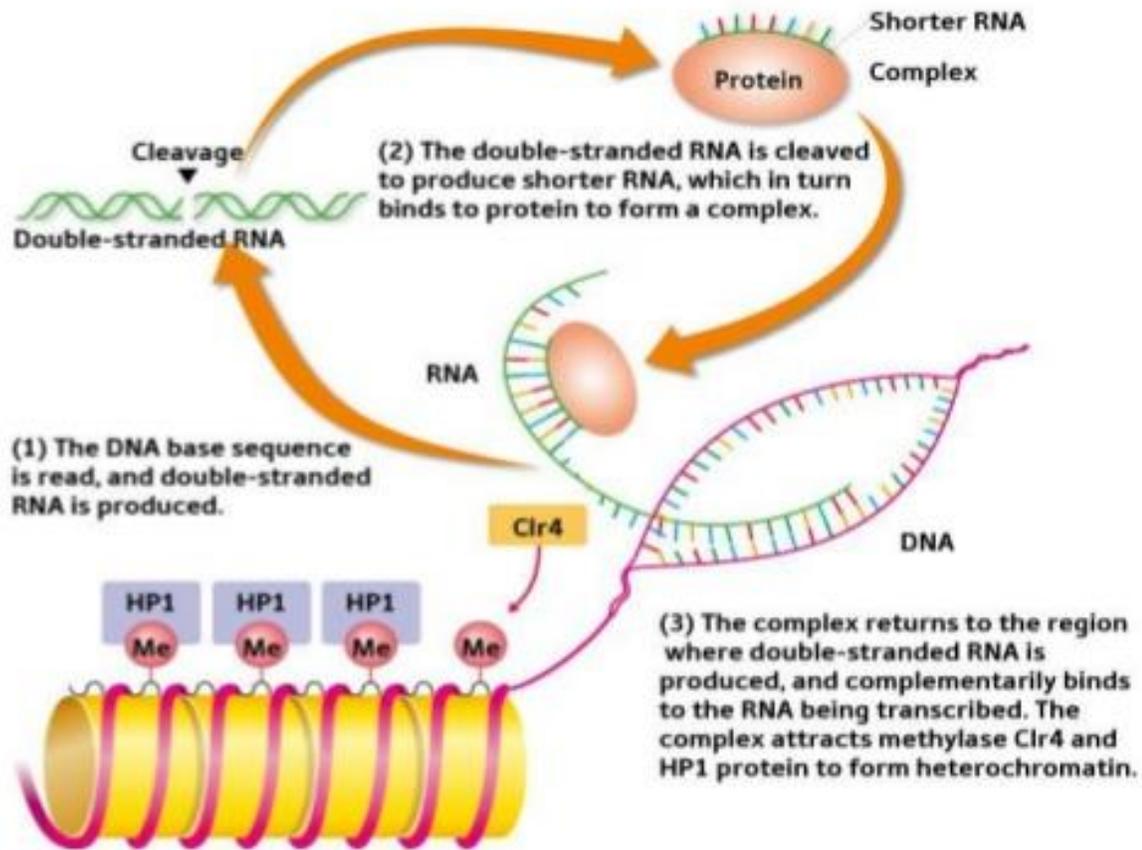
Hierarchy of Stem Cells



Genes Can be Silenced by RNA Interference

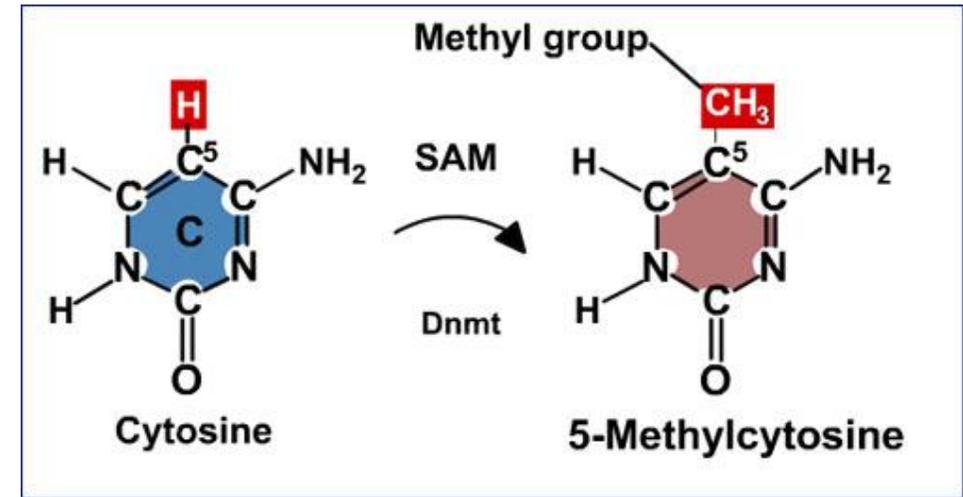
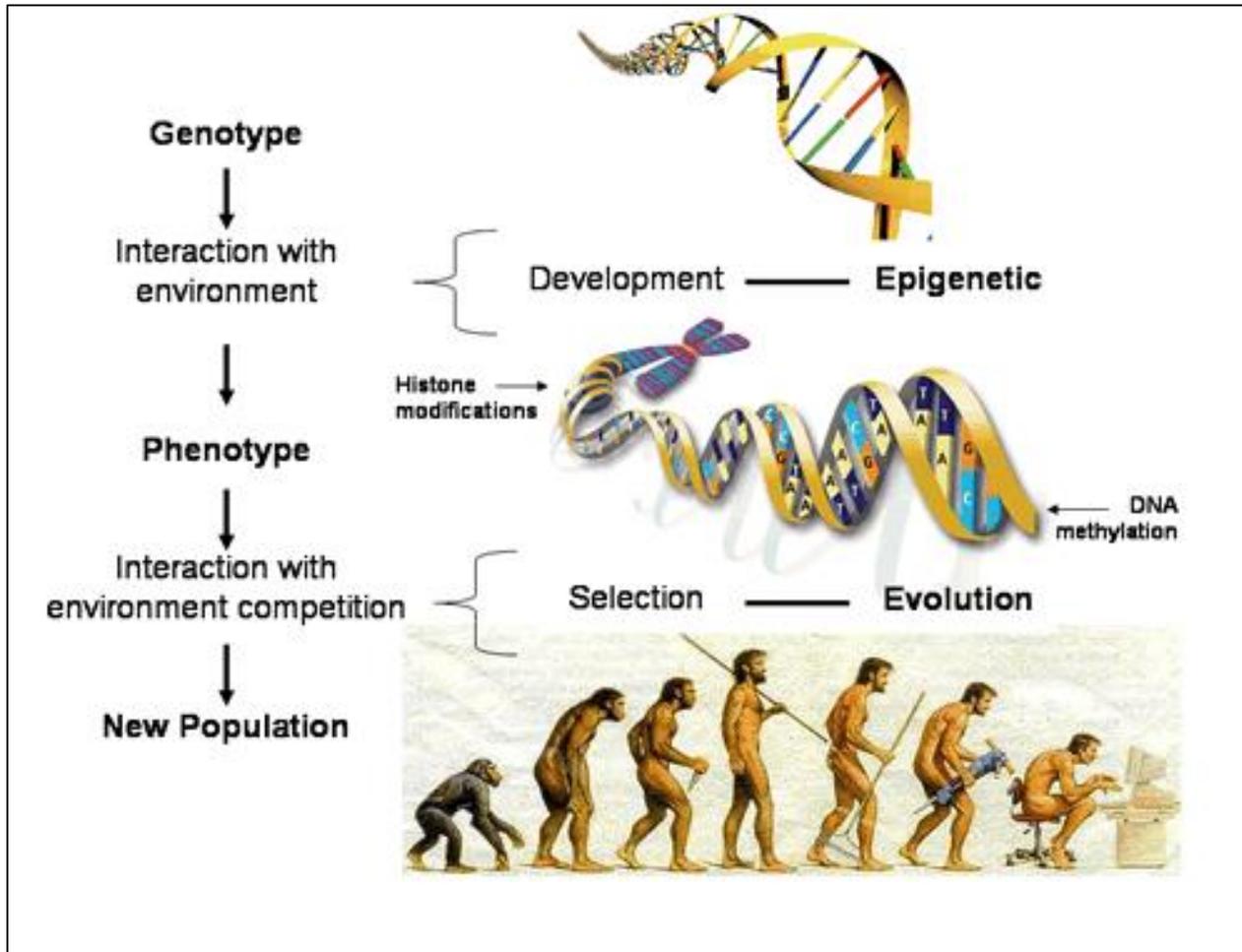
RNA interference – gene silencing by small non-coding RNAs.

The non-coding RNAs interfere with protein synthesis machinery of the cell, silencing a gene.

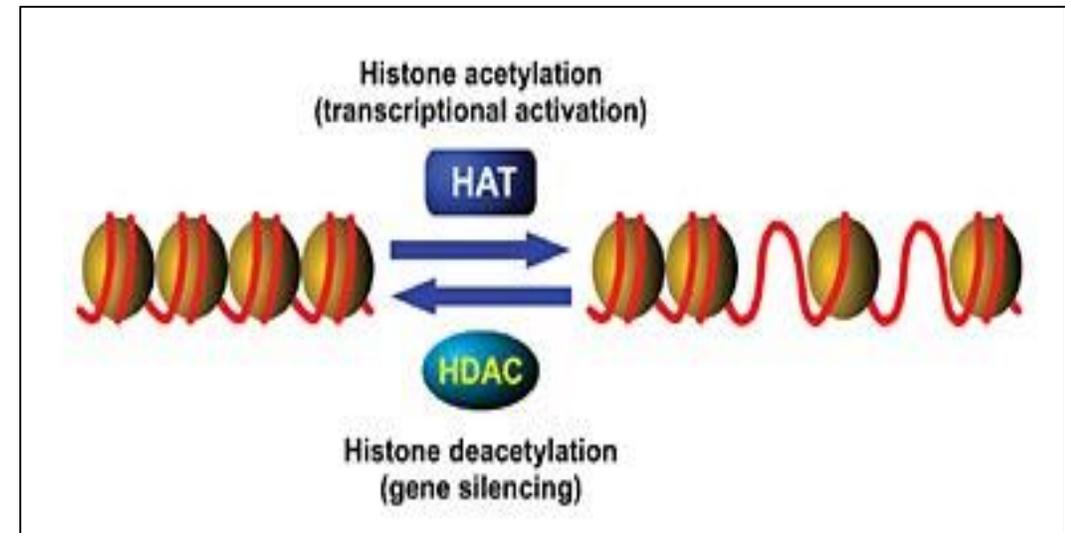


Epigenetic Modification of Gene Expression

Two Major Molecular Mechanisms: DNA Methylation & Histone Modification



DNA Methylation on Cytosine, C5

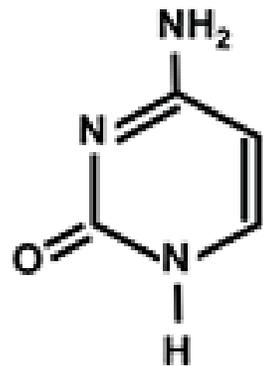
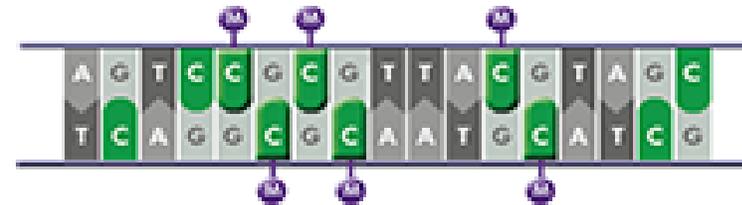


Histone Modification – Gene Activation / Silencing

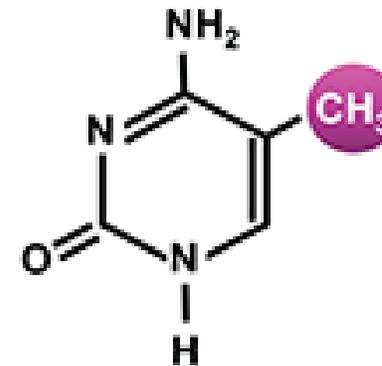
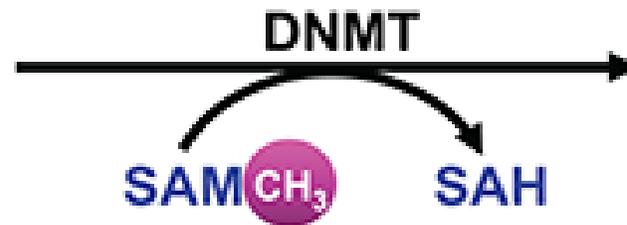
Epigenetics – Methylation of Cytosine to Control Gene Expression

DNA Methylation

Methylating the cytosine of a CpG motif silences genes



Cytosine



5' Methyl-cytosine

Environmental Epigenetic Mechanisms & Health End Points...

- **Developmental**

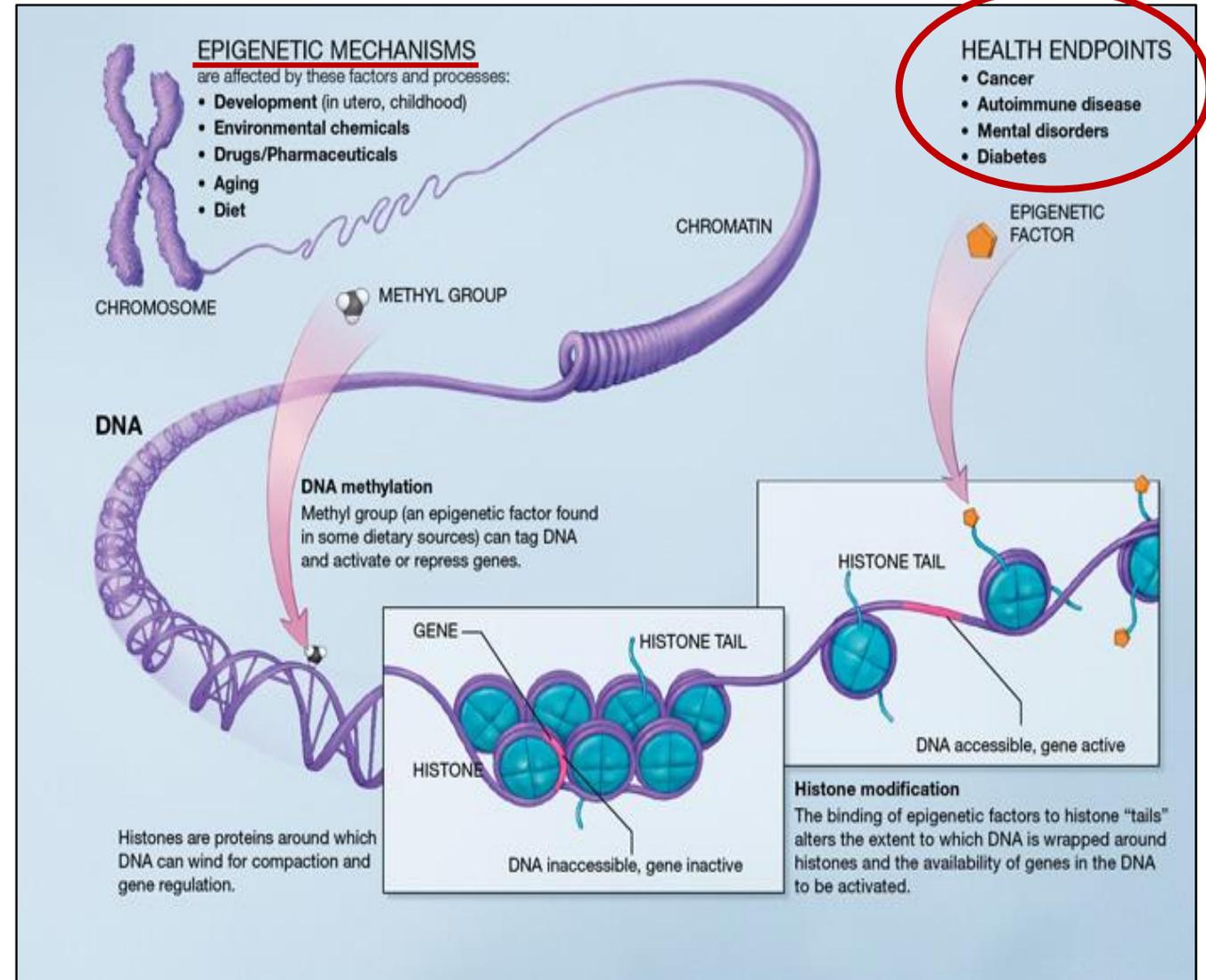
- Embryonic (*in utero*)
- Childhood
- Adolescence

- **Environmental**

- Chemicals
- Drugs/Pharmaceuticals

- **Aging / Diet**

- Nutrition/delayed aging
- Impaired DNA methylation
- Increased tumor incidence



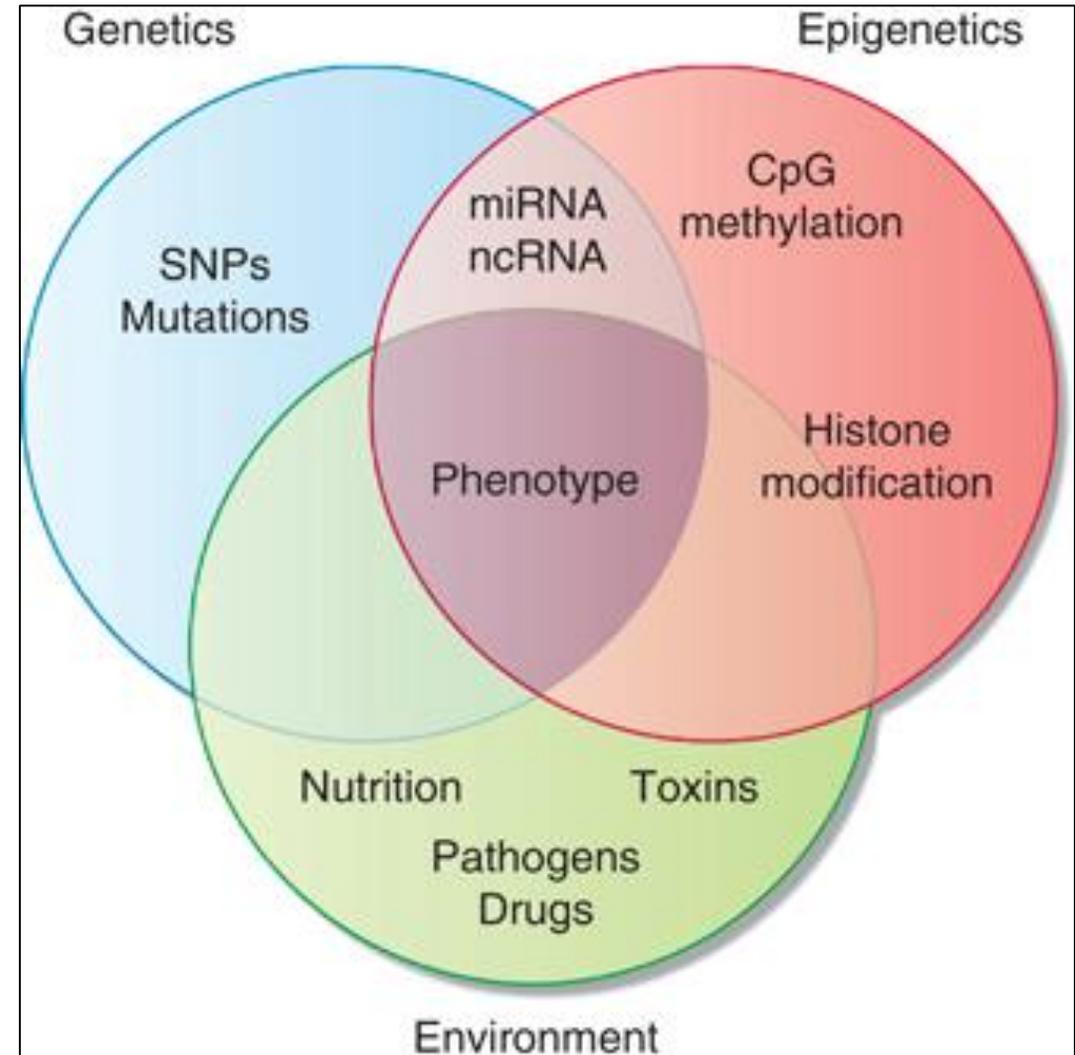
Phenotypic Nexus of Genetics, Epigenetics and Environment...

The **Genotype** of an individual organism is defined by the **collection of genes** it possesses

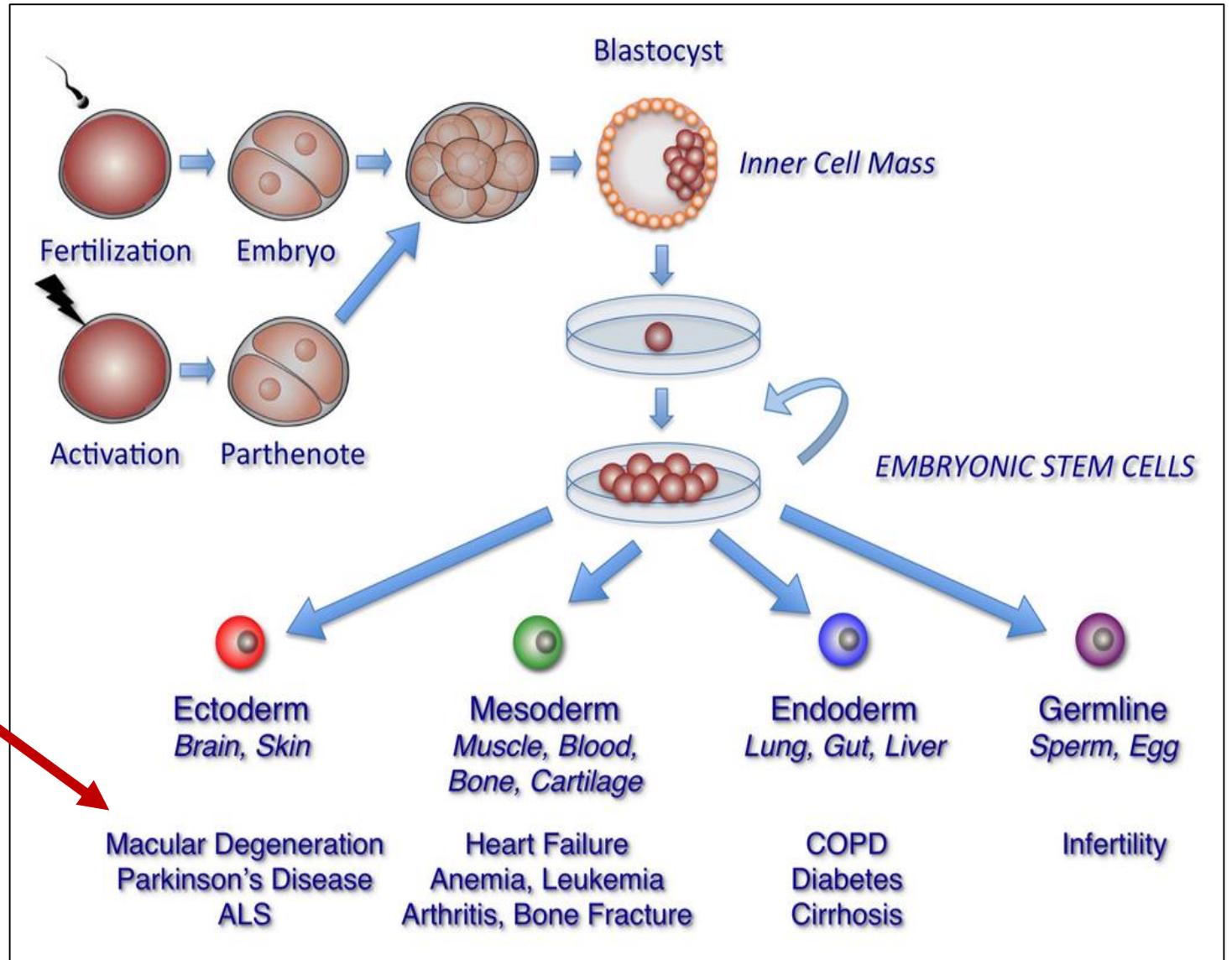
The **Phenotype** of an individual organism is the sum total of its **gene expression**, which is governed by internal **epigenetic factors** and modified by the external **environment** in which it resides

Genetic and Epigenetic Factors:

- SNPs – Single Nucleotide Polymorphisms
- miRNA – MicroRNA gene regulator
- ncRNA – Non-coding RNA gene regulator
- Epigenetic CpG methylation
- Epigenetic histone modification
- Nutrition/Toxins
- Pathogens/Drugs

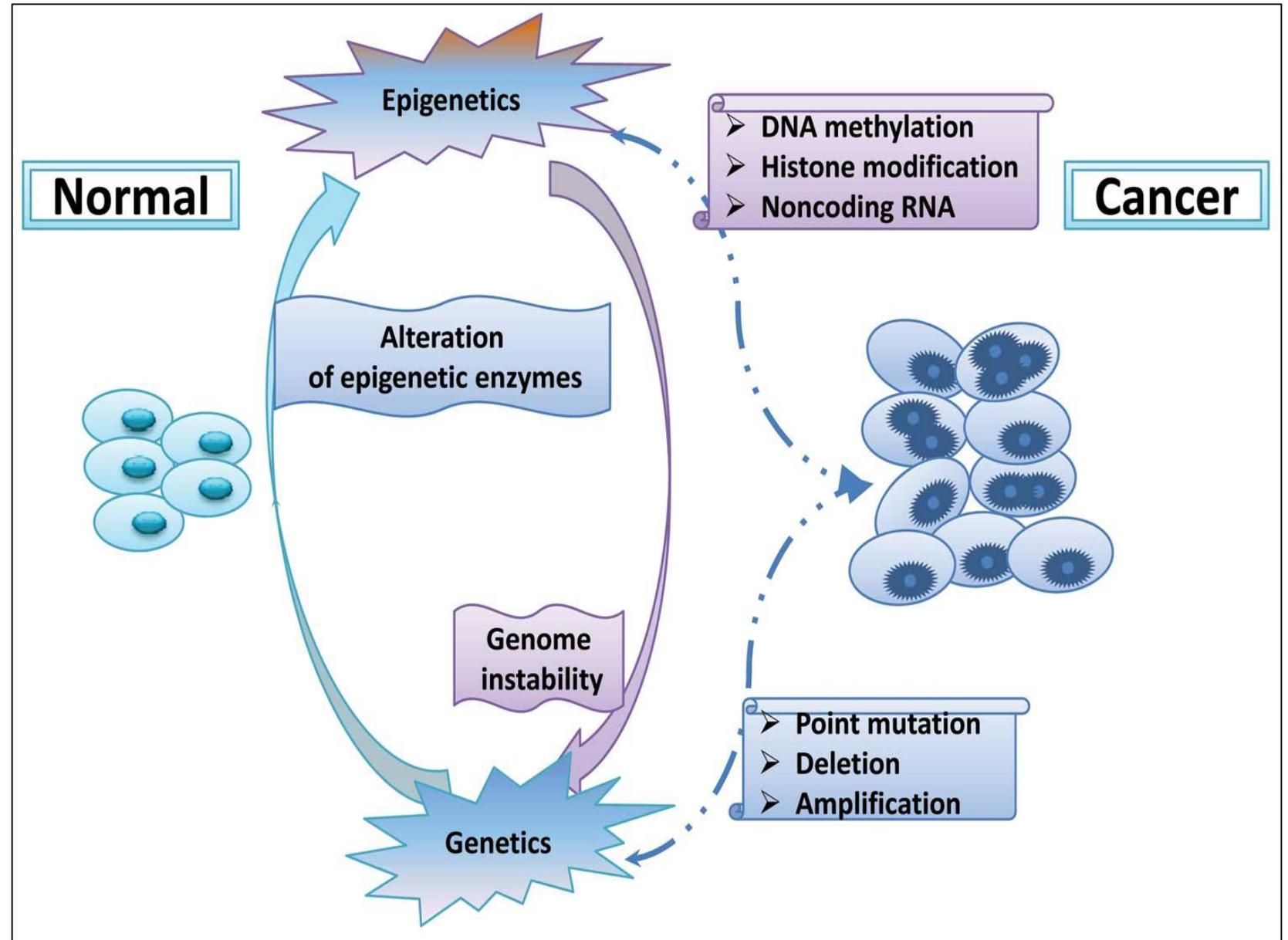


**Relationship
of
Embryonic Stem Cells,
Cellular Differentiation
and
Human Diseases...**

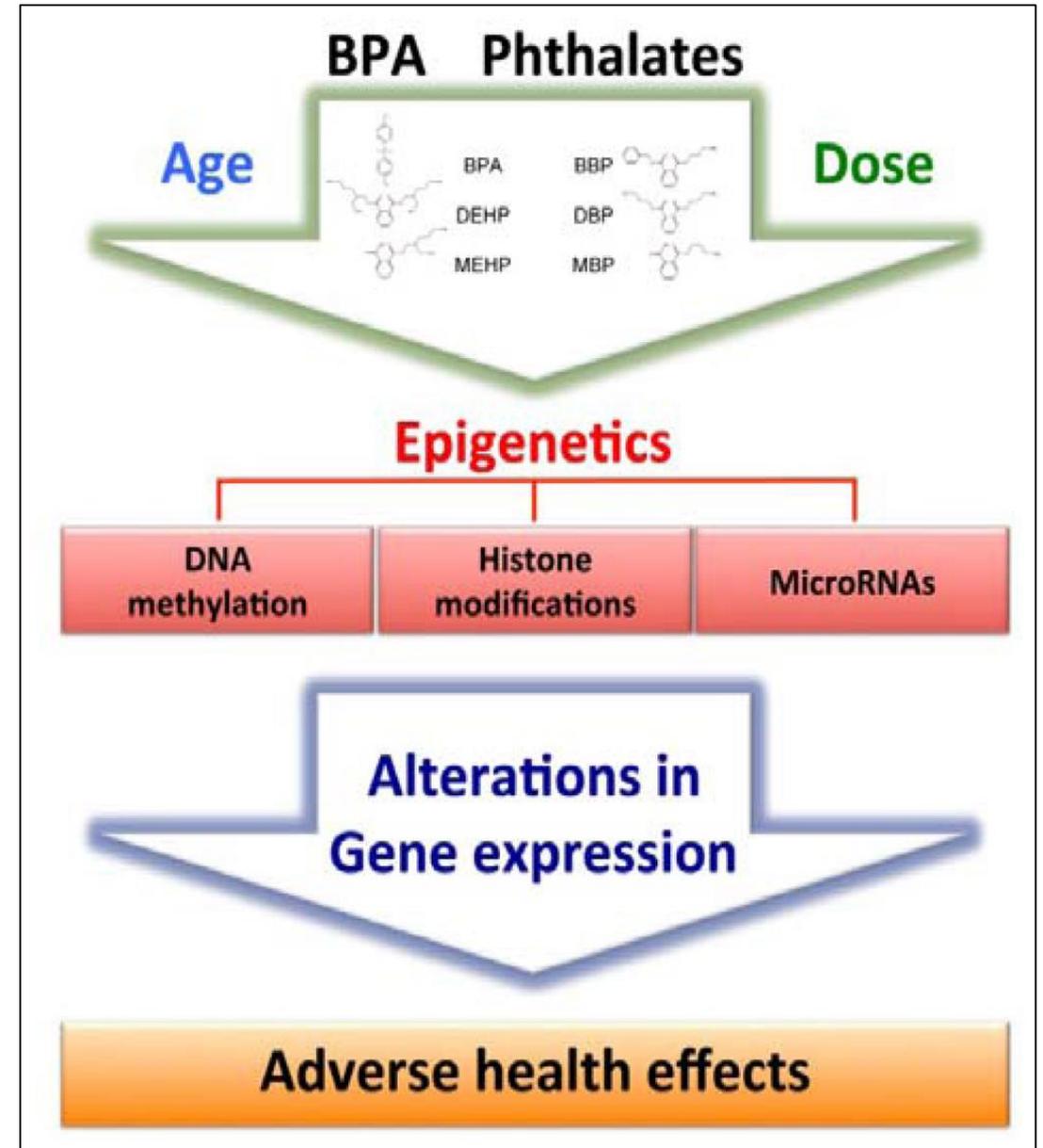
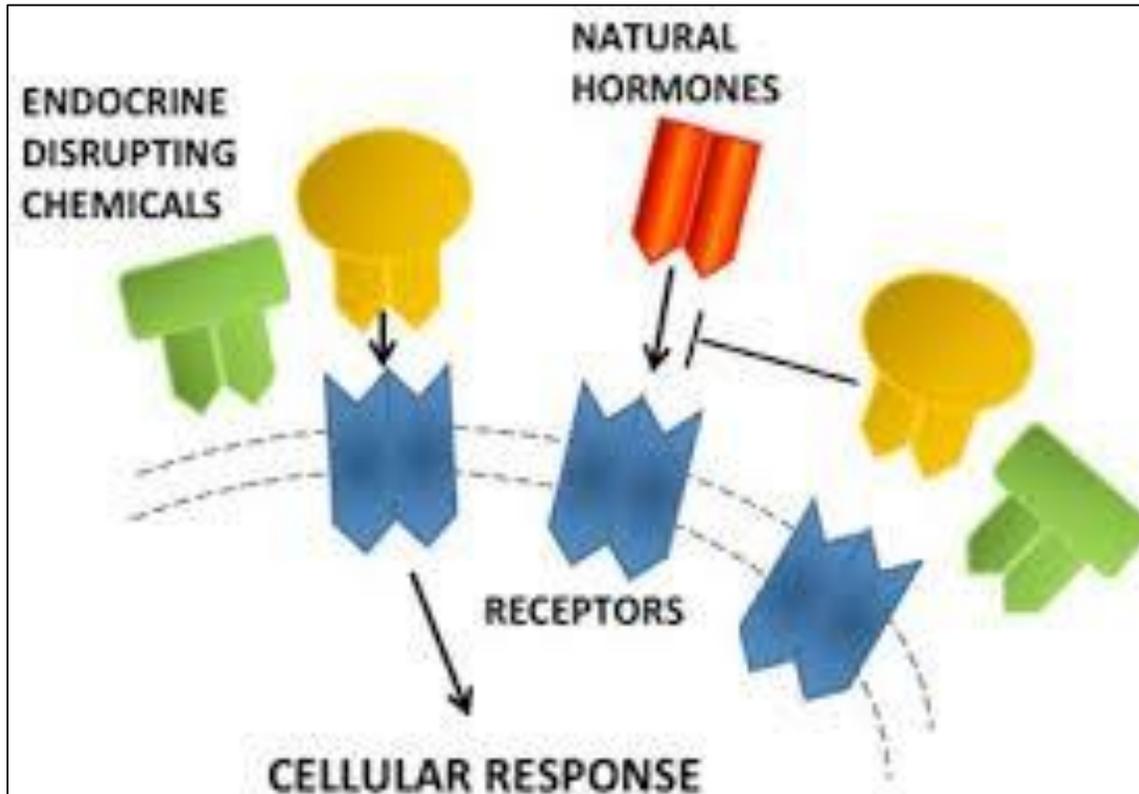


Transformation of Normal Cells to Cancerous Cells...

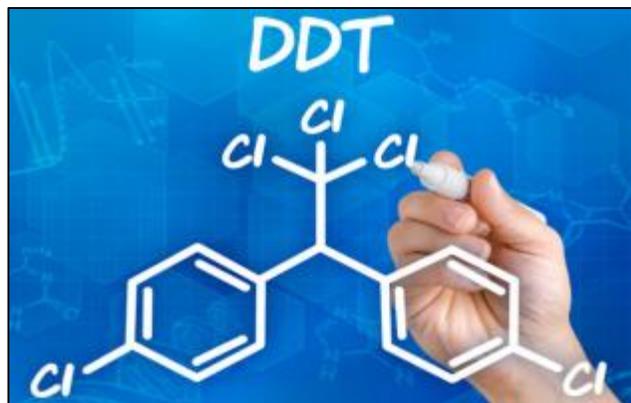
- **Genetics**
 - Point Mutation
 - Deletion
 - Amplification
- **Epigenetics**
 - DNA Methylation
 - Histone Modification
 - Noncoding RNA



Epigenetics and Endocrine Disrupting Chemicals...



M. Collotta, P. A. Bertazzi and V. Bellati,
“**Epigenetics and Pesticides**”,
Toxicology, **307**:35 – 41 (2013)



*Pesticides, a wide class of environmental contaminants, may cause both acute and delayed health effects in exposed subjects. . . Epigenetics is the study of heritable changes in gene expression that occur without a change in the DNA sequence. Several epigenetic mechanisms, including DNA methylation, histone modifications and microRNA expression, can be triggered by environmental factors. **We review current evidences indicating that epigenetic modifications may mediate pesticide effects on human health.***

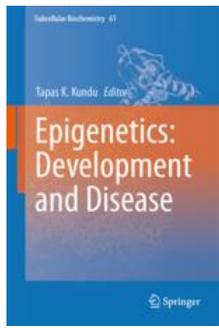
In vitro, animal, and human investigations have identified several classes of pesticides that modify epigenetic marks, including endocrine disruptors, persistent organic pollutants, arsenic, several herbicides and insecticides.

*Several investigations have examined the effects of environmental exposures and epigenetic markers, and identified toxicants that modify epigenetic states. These modifications are similar to the ones found in pathological tissue samples. In spite of the current limitations, **available evidence supports the concept that epigenetics holds substantial potential for furthering our understanding of the molecular mechanisms of pesticides health effects, as well as for predicting health-related risks due to conditions of environmental exposure and individual susceptibility.***

M. Collotta, et al., *Toxicology*, **307**:35 – 41 (2013)
(continued)

**Epigenetic Modifications Induced by Pesticides
(Table 1, adapted)**

Pesticide	Epigenetic Modification	Toxicity Test
Methoxychlor	DNA methylation	Rat
Vinclozoin	DNA methylation	Mouse embryo
DDT	DNA methylation	Rat
Persistent Organic Pollutants (DDT, BHC, Chlordane, Mirex, PCBs)	DNA methylation	Human
Arsenic	DNA methylation	In vitro
Paraquat	Histone modification	In vitro
Dieldrin	Histone modification	In vitro
Propoxur	Histone modification	In vitro
Dichlorovos	MicroRNA expression	In vitro
Fipronil, Triazophos	MicroRNA expression	Zebrafish



Epigenetics, Environment and Human Health



Summary

- Epigenetic mechanisms govern the **expression of genes** in a cell without change in its genetic code
- Several **epigenetic mechanisms** have been identified, which are modified by a variety of **environmental agents/factors** leading to human disease:
 - DNA methylation
 - Histone modification
 - Micro- and Non-coding-RNA expressions
- Epigenetic mechanisms are expressed along **two** genetic pathways:
 - **Cellular differentiation** (somatic cells – short term)
 - **Inheritable gene expression** (germ cells – long term)