

Chapter 31: Epigenetic Effects Are Inherited

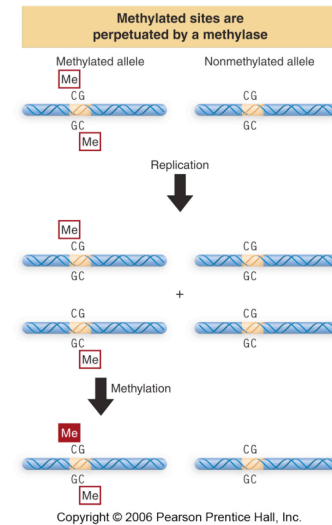
- **Epigenetic changes**
 - influence the phenotype without altering the genotype.
 - Not a mutation or change in DNA sequence
- Epigenetic effects can result from modification of a nucleic acid after it has been synthesized
 - Histone Acetylation
 - Histone methylation
 - Histone phosphorylation
 - DNA methylation
- They consist of changes in the properties of a cell that are inherited but that do not represent a change in genetic information.

Replication of a methylated site produces hemimethylated DNA in which only the parental strand is methylated.

A perpetuation methylase recognizes hemimethylated sites and adds a methyl group to the base on the daughter strand.

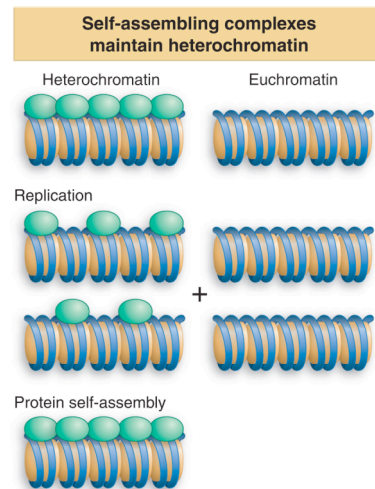
This restores the original situation, in which the site is methylated on both strands.

A nonmethylated site remains nonmethylated after replication.



Heterochromatin is created by proteins that associate with histones.

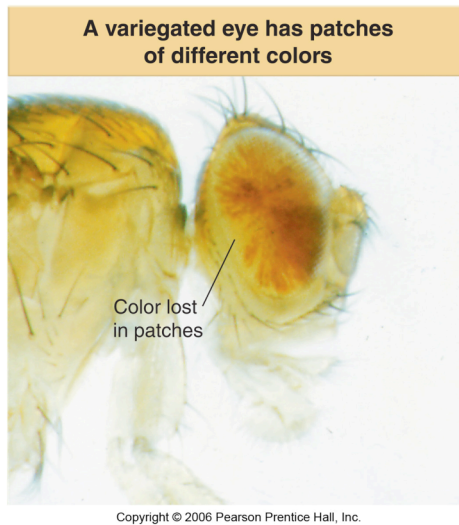
Perpetuation through division requires that the proteins associate with each daughter duplex and then recruit new subunits to reassemble the repressive complexes.



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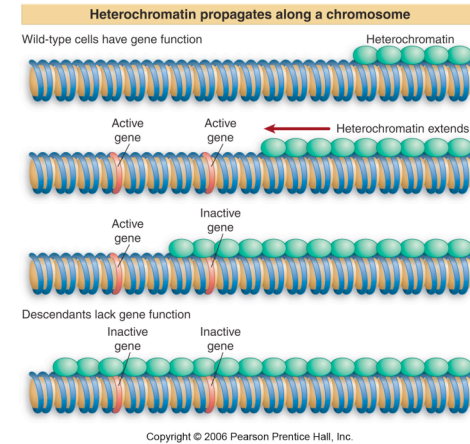
31.2 Heterochromatin Propagates from a Nucleation Event

- Heterochromatin is
 - nucleated at a specific sequence and
 - the inactive structure propagates along the chromatin fiber
- Genes within regions of heterochromatin are inactivated
- Because the length of the inactive region varies from cell to cell,
 - inactivation of genes in this vicinity causes position effect variegation.
 - **Position effect variegation (PEV)** is silencing of gene expression that results from proximity to heterochromatin.
- Similar spreading effects occur at telomeres and at the silent cassettes in yeast mating type.
 - **Telomeric silencing** describes repression of gene activity in the vicinity of a telomere.



Extension of heterochromatin inactivates genes.

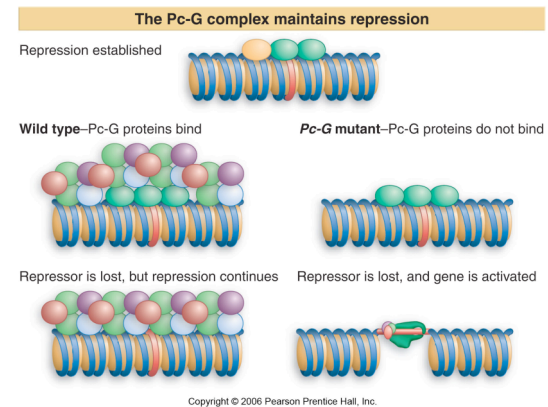
The probability that a gene will be inactivated depends on its distance from the heterochromatin region.



31.3 Polycomb and Trithorax Are Antagonistic Repressors and Activators

- Polycomb group proteins (Pc-G) perpetuate a state of repression through cell divisions.
- The PRE is a DNA sequence that is required for the action of Pc-G; it provides a nucleation center from which Pc-G proteins propagate an inactive structure.
- No individual Pc-G protein has yet been found that can bind the PRE.
- Trithorax group proteins antagonize the actions of the Pc-G.













Pc-G proteins do not initiate repression, but are responsible for maintaining it.



31.4 X Chromosomes Undergo Global Changes

- One of the two X chromosomes is inactivated at random in each cell during embryogenesis of female eutherian mammals.
 - Not the same X in all cells
 - Some are maternal X inactivated
 - Some are paternal X inactivated
- In exceptional cases where there are >2 X chromosomes, all but one are inactivated.
- Dosage compensation** describes mechanisms employed to compensate for the discrepancy between the presence of
 - two X chromosomes in one sex (female XX)
 - but only one X chromosome (male XY) in the other sex.

Different means of dosage compensation are used to equalize X chromosome expression in male and female.

Dosage compensation changes X expression			
	Mammals	Flies	Worms
	Inactivate one ♀ X	Double expression ♂ X	Halve expression ♀ 2X
X			
X			
X			
Y			

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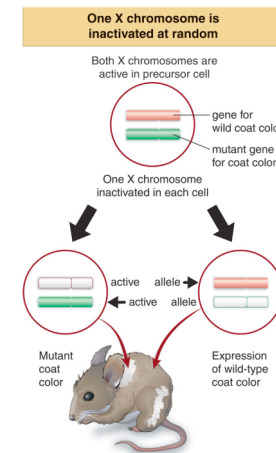
31.4 X Chromosomes Undergo Global Changes

- Facultative heterochromatin** describes the inert state of sequences that also exist in active copies—
 - for example, one X chromosome in mammalian females.
- The **single X hypothesis** describes the inactivation of one X chromosome in female mammals.
- The **n – 1 rule** states that only one X chromosome is active in female mammalian cells; any others are inactivated.
- Constitutive heterochromatin** describes the inert state of permanently nonexpressed sequences, usually satellite DNA.

X-linked variegation is caused by the random inactivation of one X chromosome in each precursor cell.

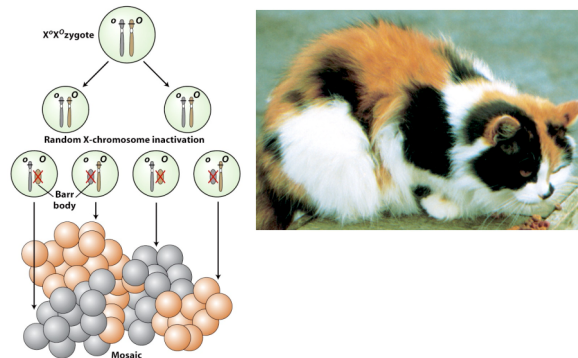
Cells in which the + allele is on the active chromosome have wild-type phenotype,

but cells in which the - allele is on the active chromosome have mutant phenotype.

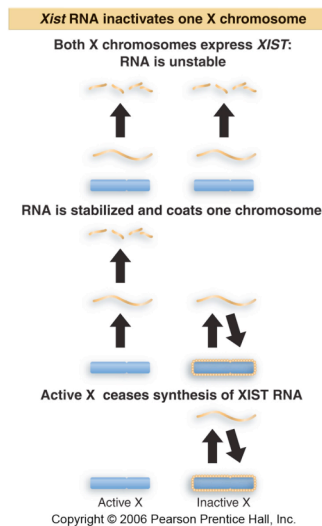


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X Inactivation Example



X-inactivation involves stabilization of *Xist* RNA, which coats the inactive chromosome.



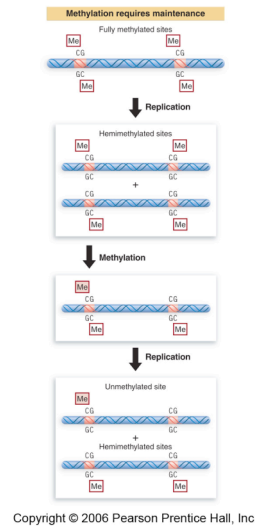
31.4 X Chromosomes Undergo Global Changes

- The *Xic* (X inactivation center) is a *cis*-acting region on the X chromosome that is necessary and sufficient to ensure that only one X chromosome remains active
- *Xic* includes the *Xist* gene, which codes for an RNA that is found only on inactive X chromosomes
- The mechanism that is responsible for preventing *Xist* RNA from accumulating on the active chromosome is unknown.
- Specific condensins are responsible for condensing inactive X chromosomes in *C. elegans*.

31.5 DNA Methylation Is Perpetuated by a Maintenance Methylase

- Most methyl groups in DNA are found on cytosine on both strands of the CpG doublet
- Replication converts a fully methylated site to a hemimethylated site.
- Hemimethylated sites are converted to fully methylated sites by a maintenance methylase.
- A **fully methylated** site is a palindromic sequence that is methylated on both strands of DNA
- **Hemimethylated** DNA is methylated on one strand of a target sequence that has a cytosine on each strand.

Hypothesis:
The state of methylated sites could be perpetuated by an enzyme that recognizes only hemimethylated sites as substrates.

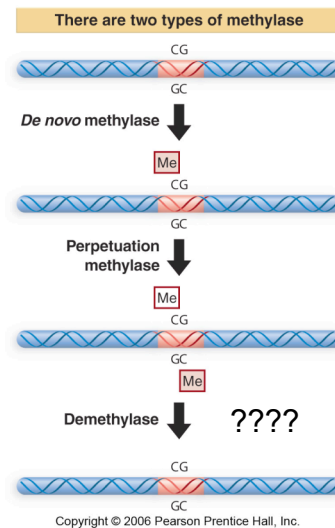


31.5 DNA Methylation Is Perpetuated by a Maintenance Methylase

- A **demethylase** is a casual name for an enzyme that removes a methyl group, typically from DNA, RNA, or protein
- A **methyltransferase (methylase)** is an enzyme that adds a methyl group to a substrate, which can be a small molecule, a protein, or a nucleic acid
- A **de novo methylase** adds a methyl group to an unmethylated target sequence on DNA.
- A **maintenance methylase** adds a methyl group to a target site that is already hemimethylated.

The state of methylation is controlled by three types of enzyme.

De novo and perpetuation methylases are known, but demethylases have not been identified.



31.6 DNA Methylation Is Responsible for Imprinting

- **Imprinting** describes
 - a change in a gene or change in gene expression
 - occurs during passage through the sperm or egg
 - results in the paternal and maternal alleles having different properties (differences in gene expression) in the very early embryo.
- This is caused by methylation of DNA.

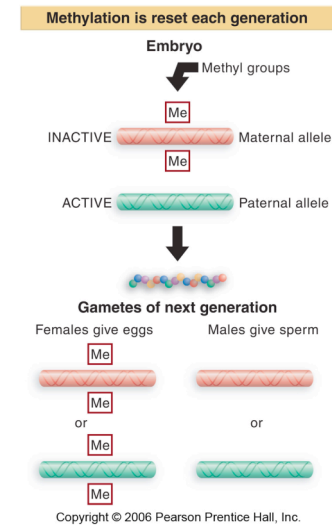
31.6 DNA Methylation Is Responsible for Imprinting

- Paternal and maternal alleles may have different patterns of methylation at fertilization
 - Methylation is usually associated with inactivation of the gene
- When genes are differentially imprinted, survival of the embryo may require that the functional allele is provided by the parent with the unmethylated allele
- Imprinted genes are present in clusters and may depend on a local control site where *de novo* methylation occurs unless specifically prevented.
- Imprinted genes are controlled by methylation of *cis*-acting sites.

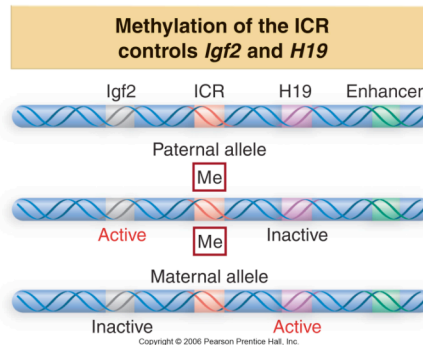
The typical pattern for imprinting is that a methylated locus is inactive.

If this is the maternal allele, only the paternal allele is active, and is essential for viability.

The methylation pattern is reset when gametes are formed, so that all sperm have the paternal type, and all oocytes have the maternal type.



- ICR is methylated on the paternal allele, where *Igf2* is active and *H19* is inactive.
- ICR is unmethylated on the maternal allele, where *Igf2* is inactive and *H19* is active.



The ICR is an insulator that prevents an enhancer from activating *Igf2*.

The insulator functions only when it binds CTCF to unmethylated DNA.

